EXHIBIT 1

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

GILDA HAGAN-BROWN, Plaintiff, v. ELI LILLY AND COMPANY, an Indiana corporation, Defendant.	Case No. 1:14-CV-01614-AJT-JFA Hon. Anthony J. Trenga **PLAINTIFF'S NOTICE TO TAKE VIDEOTAPED ORAL DEPOSITION PURSUANT TO FED. R. CIV. P. 30(b)(6)**

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE THAT pursuant to Rule 26 and 30(b)(6) of the Federal Rules of Civil Procedure, Plaintiff, by and through their undersigned attorneys, will take the deposition of those employees and/or agents of Eli Lilly and Company ("Lilly") who are described in the accompanying Exhibit A, beginning on Monday, April 20, 2015, at 9 a.m., and to continue day to day, Sundays and holidays excepted, until completed. The deposition(s) will be held at the law offices of Baum Hedlund Aristei & Goldman, P.C., located at 12100 Wilshire Blvd., Ste. 950, Los Angeles, CA 90025. Pursuant to Fed. R. Civ. P. 30(b)(6), Lilly shall designate and produce a designated representative or representatives, as may be required, to testify on behalf of Lilly concerning the topics identified in Exhibit A attached hereto. The deposition will be taken before a person authorized by law to administer oaths, pursuant to Fed. R. Civ. P. 28, and may also be videotaped.

Dated: March 24, 2015

Respectfully submitted,

BAUM HEDLUND ARISTEI & GOLDMAN, P.C.

/s/ R. Brent Wisner

R. Brent Wisner, Esq. (*pro hac vice*)
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MILLER LEGAL, LLC

/s/ Brielle M. Hunt

Brielle M. Hunt, Esq.
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Attorneys for Plaintiff

EXHIBIT A

I. DEFINITIONS

1. "LILLY" refers to Eli Lilly and Company, the manufacturer of Cymbalta.

2. "CYMBALTA" OR "DULOXETINE" means duloxetine hydrochloride, including any other name or trademark under which it is sold, domestically *or* abroad, marketed or produced, including products sold, marketed, or produced by others if they do so with your permission, at your request, at your direction, with your acquiescence, and/or if you gain any benefit from their sales, marketing, or distribution.

3. "DOCUMENT" refers to every original, draft and duplicate of every writing and recording of every type and description, including, but not limited to, all writings, recordings, electronically stored information, electronic writings (such as information contained on the internet), e-mail, intra- or inter-company communications, memoranda, reports and photographs as those terms are defined in Rule 1001 of the Federal Rules of Evidence and all documents or tangible things as those terms are used in Rule 34 of the Federal Rules of Civil Procedure.

4. The term "WITHDRAWAL" includes discontinuation or tapering, as well as DEAEs, withdrawal symptoms, and any side effects of withdrawing, discontinuing, or tapering from CYMBALTA.

5. The term "DEAE" means Discontinuation Emergent Adverse Event, and refers to any possible side effects or symptoms relating to discontinuing, withdrawing, or tapering from the use, consumption, or treatment with Cymbalta.

6. The term "PERAHIA ARTICLE" refers to David G. Perahia, *et al.*, *Symptoms Following Abrupt Discontinuation of Duloxetine Treatment in Patients with Major Depressive Disorder*, 89 J. Affective Disorders 207-12 (2005).'

7. The "FDA" is the U.S. Food and Drug Administration.

8. The phrase "European label" refers to the European Medicines Agency Summary of Product Information for Cymbalta.

9. The phrase "U.S. Label" refers to the FDA-approved product insert for Cymbalta.

II. SUBJECT MATTER OF DEPOSITIONS

Pursuant to Rule 30(b)(6), LILLY shall designate and produce for deposition one or more of its officers, directors, managing agents, or other persons who consent to testify on its behalf concerning the following subject matters:

A. Clinical Trials

1. All clinical trials identified in Lilly's response to RFP No. 61 and all clinical trials, whether placebo-controlled, active-controlled, or open-label that measured DEAEs associated with Cymbalta. For clarity, the witness should be able to testify with regard to the following:

a. The design of the trials, including inclusion and exclusion criteria, informed consent DOCUMENTS or procedures, primary and secondary outcomes of interest, rating mechanisms, controls, and "powering";

b. The results and outcome of the trials;

c. The publication and/or public availability of the results and date of the trial, to include (i) whether the results of the trial have been provided to the FDA, (ii) whether the results have been published, in whole or in part, in the scientific literature, and (iii) whether Lilly has either considered or implemented a plan to post the trial results in a clinical trial registry on the Internet;

d. The identity of those former and current consultants and employees responsible

for the design, execution, and analysis of the trial, including locations of testing centers, consultants, statisticians, and ethicists, and for former employees and consultants, information about how the relationship terminated.

B. European Labeling for Cymbalta

1. The creation, development, writing, and approval of the European Medicines Agency Summary of Product Information for Cymbalta. For clarity, the witness should be able to testify with regard to the following:

a. Why the rate of patients experiencing at least one DEAE reflected in the Perahia article was included in the European label.

b. Why the words "withdrawal symptoms" were used in the European label rather than the words "discontinuation symptoms" in the U.S. Label.

c. Why the duration of "withdrawal symptoms" in the European label is described differently from the duration of "discontinuation symptoms" described in the U.S. Label.

d. Why the instruction "duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks" was included in the European label.

e. Who and how Lilly communicated with the European Medicines Agency (or its predecessor, the European Agency for the Evaluation of Medicinal Products) pertaining to the European label.

f. The process by which the Marketing Authorization Application (MAA), and any and all supplements thereto, was prepared and submitted by Lilly to the European Medicines Agency (or its predecessor, the European Agency for the Evaluation of Medicinal Products).

g. The organization, structure, personnel, and document preparation and retention

policies of Lilly's Global Product Labeling Committee (GPLC).

h. The process by which all versions of the European SPC (Summary of Product Characteristics) was prepared and submitted by Lilly to the European Medicines Agency (or its predecessor, the European Agency for the Evaluation of Medicinal Products), and the custodian(s) thereof.

i. The process by which all versions of the RAPT (Regulatory Activity and Planning Tracker) was prepared and maintained by Lilly, and the custodian(s) thereof.

j. Who and how Lilly communicated with the CHMP (Committee for Medicinal Products for Human Use).

k. Who and how Lilly communicated with the European "Rapporteur," including (but not limited to) the 2005 Rapporteur assessment of Lilly's second periodic safety update report (PSUR).

C. Lilly's Marketing Relationship with WebMD

1. All marketing efforts made in conjunction with WebMD to promote Cymbalta or Prozac. For clarity, the witness should be able to testify with regard to the following:

a. The development of WebMD's various symptom checkers and screening platforms related to depression, fibromyalgia, or chronic pain.

b. All contractual terms between Lilly and WebMD.

c. Senator Charles Grassley's investigation of Lilly's relationship with WebMD.

d. The marketing analytics associated with Lilly's WebMD marketing efforts.

D. The Cymbalta Capsule

1. The design and dosing of the Cymbalta capsule. For clarity, the witness should be able to testify with regard to the following:

a. Why was a 20 mg dose of Cymbalta created. Who was responsible for making decisions about the available dosing levels for Cymbalta.

b. Why is the Cymbalta capsule in an enteric coating. Why was Cymbalta designed in a capsule form? How do the pellets within the Cymbalta capsule work in the absorption of the drug.

c. Why does the Cymbalta label advise against opening the Cymbalta capsule? What safety / efficacy concerns are associated with ingestion of Cymbalta outside of the capsule?

d. Were smaller doses, i.e., 10 or 5 mg ever considered? If so, why were they never created?

CERTIFICATE OF SERVICE

I hereby certify that on this 24th day of March, 2015, a true and correct copy of the foregoing PLAINTIFF'S NOTICE TO TAKE VIDEOTAPED ORAL DEPOSITION PURSUANT TO FED. R. CIV. P. 30(b)(6) was served via Electronic Mail, upon the following:

Michael X. Imbroscio
mimbroscio@cov.com
Phyllis A. Jones
pajones@cov.com
Jeffrey T. Bozman
jbozman@cov.com
COVINGTON & BURLING LLP
One City Center
850 Tenth Street, NW
Washington, DC 20001

Attorneys for Eli Lilly and Company

Samantha Jison

EXHIBIT 2

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

JANINE ALI, Plaintiff, v. ELI LILLY AND COMPANY, an Indiana corporation, Defendant.	Case No. 1:14cv-01615-AJT-JFA Hon. Anthony J. Trenga **PLAINTIFF'S NOTICE OF DEPOSITION OF TORKIL FREDBORG**

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE THAT pursuant to Rules 30 and 45 of the Federal Rules of Civil Procedure, Plaintiff Janine Ali, by and through undersigned counsel, will take the oral deposition of Torkil Fredborg, **on Wednesday, April 22, 2015** commencing at **9:00 a.m** and will continue from day to day until completed. The deposition will take place at the law offices of Baum Hedlund Aristei & Goldman, P.C., located at 12100 Wilshire Blvd., Ste. 950, Los Angeles, California 90025. The deposition will be recorded stenographically and by videotape and is to be taken pursuant to the Federal Rules of Civil Procedure and other applicable laws, and for all lawful purposes, including trial.

Pursuant to the pertinent provisions of the Federal Rules of Civil Procedure, Mr. Fredborg is requested to produce at his deposition the records, documents, and tangible items set forth in the attached Exhibit A.

Dated: March 23, 2015

Respectfully submitted,

BAUM HEDLUND ARISTEI & GOLDMAN, P.C.

/s/ R. Brent Wisner

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MILLER LEGAL, LLC

/s/ Brielle M. Hunt

Brielle M. Hunt, Esq.
Peter Miller, Esq.
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Fax: (800) 768-9542
Email: bhunt@millerlegalllc.com

Attorneys for Plaintiff

EXHIBIT A

I. DEFINITIONS

1. The term "DOCUMENT" shall have the broadest meaning possible under Rule 34 of the Federal Rules of Civil Procedure and includes all originals and drafts, in any and all languages, of any nature whatsoever, in your possession, custody or control, regardless of where located, and include, but are not limited to, letters, correspondence, logs, drafts, contracts, prospective contracts, agreements, reports, records, studies, surveys, resolutions, tabulations, notes, summaries, memoranda, Electronically Stored Information ("ESI"), electronic mail ("email"), calendar or diary entries, handwritten notes, working papers, work sheets, spread sheets, diagrams, minutes of meetings, agendas, bulletins, periodicals, circulars, advertisements, notices, announcements, invoices, statements, checks (front and back), bank statements, ledgers, orders, vouchers, instructions, drawings, charts, graphs, manuals, brochures, pamphlets, schedules, telegrams, teletypes, photographs, audio tapes, voice-mail messages, videotapes, electronic recordings, facsimile transmissions, and information of whatever kind either stored on computers, including computer disks, hard drives and other media, or contained in any computer or information retrieval devices.

2. The term "CYMBALTA" means duloxetine hydrochloride, including any other name or trademark under which it is sold, domestically *or* abroad, marketed or produced, including products sold, marketed, or produced by others if they do so with Lilly's permission, at Lilly's request, at Lilly's direction, with Lilly's acquiescence, and/or if Lilly gained any benefit from their sales, marketing, or distribution.

3. The term "WITHDRAWAL" includes discontinuation or tapering, as well as DEAEs, withdrawal symptoms, and any side effects of withdrawing, discontinuing, or tapering from CYMBALTA or another antidepressant.

4. The term "SNRI" means serotonin norepinehprine reuptake inhibitor.

5. The term "SSRI" means selective serotonin reuptake inhibitor.

II. REQUESTS FOR PRODUCTION

1. Any and all DOCUMENTS in your possession, custody or control that address, mention, or discuss CYMBALTA WITHDRAWAL. This request includes any emails (whether personal or company-issued) and any other DOCUMENTS on your computer (whether personal or company-issued).
2. Any and all DOCUMENTS in your possession, custody or control that address, mention, or discuss SSRI AND/OR SNRI WITHDRAWAL. This request includes any emails (whether personal or company-issued) and any other DOCUMENTS on your computer (whether personal or company-issued).
3. The contents of any and all files in your possession, custody or control titled CYMBALTA WITHDRAWAL or any similarly worded title (e.g. “Cymbalta Discontinuation,” “SSRI Withdrawal,” “SNRI Discontinuation.”).

CERTIFICATE OF SERVICE

I hereby certify that on this 23rd day of March, 2015, a true and correct copy of the foregoing PLAINTIFF'S NOTICE OF DEPOSITION OF TORKIL FREDBORG was served via United States Mail and Electronic Mail, upon the following:

Michael X. Imbroscio
mimbroscio@cov.com
Phyllis A. Jones
pajones@cov.com
Jeffrey T. Bozman
jbozman@cov.com
COVINGTON & BURLING LLP
One City Center
850 Tenth Street, NW
Washington, DC 20001

Attorneys for Eli Lilly and Company

Samantha Jison

EXHIBIT 3

Wisner, R. Brent

From: Wisner, R. Brent
Sent: Wednesday, April 08, 2015 3:18 PM
To: 'Stekloff, Brian'; Broomandan, Amber
Cc: Imbroscio, Michael; Jones, Phyllis; Reynolds, Brett; pmiller@millerlegalllc.com; T. Matthew Leckman; Esfandiari, Bijan; Baum, Michael
Subject: RE: Ali and Hagan-Brown Deposition Notices

Brian,

I often work past 9:00 p.m. my time, which is past midnight your time. Not sure that has any relevance to these issues, but you felt the need to characterize my correspondence as "midnight" email so I felt the need to respond in kind.

Here are the issues we are at an impasse about and for which I will be filing an motion about this week:

1. 30(b)(6) deposition on topics of European labeling and the Cymbalta capsule design.
2. Deposition of Torkil Fredborg
3. Emails of Antonio Crucitti, Virginia Wyss, and Carol Stephens

On these issues, please let me know if Lilly would amenable to setting the hearing date for Thursday, April 16, 2015 (assuming the Court is available). As I have discussed in a separate email, Dr. Bahadori's deposition will be transpiring on the morning of Friday, April 17, 2015 so it would be better, provided the Court is amenable, to have an earlier hearing. Let me know of Lilly's position.

We will go about serving subpoenas on Virginia Wyss and Carol Stephens and Lilly can file any needed motion to quash. Do you represent Virginia Wyss and Carol Stephens and, thus, will accept service for them? Or should go about contacting these witnesses directly?

On the bates stamp, the document I am referencing is the one that starts CYM-02275917. My apologies for any confusion.

Brent

From: Stekloff, Brian [mailto:BStekloff@cov.com]
Sent: Wednesday, April 08, 2015 1:05 PM
To: Wisner, R. Brent; Broomandan, Amber
Cc: Imbroscio, Michael; Jones, Phyllis; Reynolds, Brett; pmiller@millerlegalllc.com; T. Matthew Leckman; Esfandiari, Bijan; Baum, Michael
Subject: RE: Ali and Hagan-Brown Deposition Notices

Brent:

I write in response to your April 6 midnight ET email regarding the deposition notices in Ali and Hagan-Brown. I address each remaining topic below:

Dr. Wohlreich, Dr. Detke and 30(b)(6) regarding Clinical Trials

We are working on securing dates and will seek to schedule the depositions so that they can be completed in one trip. I hope to have dates to you by the end of this week. Moreover, we are in the process of preparing Dr. Wolreich's emails and will produce them to you in advance of the deposition.

European Labeling for Cymbalta 30(b)(6) topic and Torkil Fredborg

As we have stated, we do not believe the European labeling for Cymbalta topic is appropriate for discovery in these cases, and we will oppose any motion you file on this topic. In the same vein, you've indicated that your purpose in seeking the deposition of Dr. Fredborg is to inquire about the European label. For the same reasons we oppose a deposition of a 30(b)(6) witness regarding European labeling, we oppose your request to depose Dr. Fredborg. Of course, if the Court rules in your favor on the 30(b)(6) issue that the European labeling is an acceptable topic, we will produce Dr. Fredborg as well.

The Cymbalta Capsule

We do not think you can make out a viable claim relating to the design of the Cymbalta capsule, and we will thus oppose your motion to seek a deposition on this topic.

Matthew Kuntz

We hope to speak later today to Mr. Kuntz, whom we understand is just back from vacation. As we mentioned, he is currently employed by AbbVie, but we will inquire if he is willing to appear voluntarily for a deposition, and if so, we will work to present him for testimony consistent with his schedule.

Antonio Crucitti

Dr. Crucitti is located in Italy and out of our control. We will not produce him. We also do not intend on producing his emails.

Virginia Wyss and Carol Stephens

Ms. Wyss and Ms. Stephens are both retired and thus out of our control, and we further object to their depositions. You assert that you intend on questioning both witnesses regarding the Cymbalta label and the core data sheet. Such testimony is unnecessary and cumulative. First, the language in the label and the core data sheet is not in dispute. Second, we have responded to numerous interrogatories on these topics. Third, you already have deposed Dr. Hoog, Ms. Mescher, and a 30(b)(6) witness regarding the same topics, i.e., the Cymbalta label and the core data sheet. Fourth, assuming he agrees to appear, your email indicates that you intend on questioning Mr. Kuntz on the similar topic of the United States Physicians' Package Insert. As such, we believe the depositions of these two retired employees are cumulative and unnecessary for these cases. As such, we do not intend to produce either witness' emails.

Finally, with respect to Ms. Stephens, one of the documents you reference is CYM-022275931. We do not believe this is an accurate Bates number. Can you please double-check your notes and re-send the correct Bates number?

Michael Roesner

As Mike indicated in his letter dated yesterday, we accept your compromise regarding Mr. Roesner, and we will work to produce his emails promptly.

I am available to discuss any of these issues if you would like to do so.

Brian

Brian Stekloff

Covington & Burling LLP
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COVINGTON

From: Wisner, R. Brent [mailto:rbwisner@baumhedlundlaw.com]
Sent: Monday, April 06, 2015 11:58 PM
To: Stekloff, Brian; Broomandan, Amber
Cc: Imbroscio, Michael; Jones, Phyllis; Reynolds, Brett; pmiller@millerlegalllc.com; T. Matthew Leckman; Esfandiari, Bijan; Baum, Michael
Subject: RE: Ali and Hagan-Brown Deposition Notices

Brian,

Thanks for following-up on this.

On March 24, 2015, Plaintiffs noticed the depositions of:

(1) A 30(b)(6) Notice regarding four categories:
   a. Clinical Trials
   b. European Labeling for Cymbalta
   c. Lilly's Marketing Relationship with WebMD
   d. The Cymbalta Capsule
(2) Virginia Wyss
(3) Madelaine Wohlreich
(4) Micahel Roesner
(5) Matt Kuntz
(6) Antonio Crucitti
(7) Carol Stephens
(8) Michael Detke
(9) Torkil Fredborg

It appears that Lilly does not object to three depositions: Dr. Michael Detke, Dr. Madelaine Wohlreich, and a 30(b)(6) deposition on the issue of clinical trials. Since Dr. Detke and Dr. Wohlreich are both in Indiana, it would be extremely convenient if the three depositions could be scheduled on back-to-back days so we can knock them out in one trip. Please take all efforts to secure dates for these three depositions now, so that I can get them scheduled.

For the remainder, there appears to be issues attendant to each, so here is Plaintiffs response.

30(b)(6) Depositions

A. Clinical Trials (and Madelaine Wohlreich)

It appears that Lilly does not object to the taking of a 30(b)(6) deposition relating to Cymbalta Clinical Trials. Lilly has proposed Dr. Wohlreich to speak on behalf of Lilly regarding topics identified in Plaintiff Hagan-Brown's Rule 30(b)(6) notice. You have requested that the deposition of Dr. Wohlreich (individually) be done at the same time she is deposed pursuant to Rule 30(b)(6). Unfortunately, Plaintiffs cannot accommodate this request. I do not believe both depositions can be covered in a single seven-hour sitting. Plaintiffs would be happy to schedule each deposition on back-to-back days and refrain from re-asking the same questions so as to shorten each deposition as much as possible.

In any event, Plaintiffs will need a production of Dr. Wohlreich's emails pursuant to the letter I sent on March 19, 2015. Please advise if Lilly will make such a production or whether Plaintiffs will need to file a motion with the Court.

Also, please let me know when you have two back-to-back days for the depositions to transpire.

B. European Labeling for Cymbalta

It appears Lilly will not produce a witness responsive to this issue. The fact that Lilly has chosen to state the actual risk of withdrawal on the European label and use the misleading warning of "greater than or equal to 1%" in the U.S. is highly relevant to knowledge and motive. Moreover, based on a review of the documents, the content of the U.S. product insert was not isolated to people residing in the U.S., but that there were dozens of people globally involved both in developing the U.S.P.I—the same people working on foreign labels as well. Exploring the overlap of personnel and the exchange of ideas further supports that this information is relevant to evaluating the extent and scope of Lilly's knowledge about the Cymbalta withdrawal risk. Cutting off any discovery on this issue, which is reasonably calculated to lead to relevant information is improper. We will file an appropriate motion.

C. Lilly's Relationship with WebMD

Your reading of the learned intermediary is not correct. Evidence that Lilly took steps to undermine the learned intermediary by providing medical advice directly to consumers through WebMD is highly relevant. Indeed, considering

the fact that the learned intermediary doctrine is a judicially created affirmative defense, born out of a respect to the client-patient relationship, Lilly's surreptitious efforts displace the learned intermediary would justify, on equitable grounds, the refusal to allow Lilly to assert the defense, i.e., unclean hands doctrine. However, since neither Ali or Hagan-Brown or their physicians have testified that they relied on Lilly's WebMD marketing, Plaintiffs will not pursue this topic of discovery at this time.

D. The Cymbalta Capsule

As you know, one of Plaintiffs' claims against Lilly is that the Cymbalta pill, as marketed and labeled, fails to allow for the safe discontinuation of Cymbalta. The smallest dose is 20 mg and the label expressly forbids patients from opening the capsule to concocted a smaller dose. Thus, no matter what tapering regimen is prescribed, at some point every patient who ever attempts to discontinue Cymbalta will need to quit 20 mg cold turkey. There is a 20 mg cliff. Lilly's failure to provide smaller doses or to design a capsule that could be altered to allow for safe discontinuation or to simply warn patients that there was this 20 mg cliff qualifies as both a design defect *and* failure to warn. The cases you cite relate to claims against generic manufacturers being preempted. They have nothing to do with the claims alleged here. *See generally*, *Wyeth v. Levine*, 555 U.S. 555 (2009) (which governs state law claims against <u>*brand name*</u> manufacturers). Indeed, the only decision to come out involving preemption and Cymbalta withdrawal flatly rejected these meritless preemption challenges. *Saavedra v. Eli Lilly & Co.*, No. 2:12-CV-9366-SVW-MAN, 2013 WL 3148923 (C.D. Cal. June 13, 2013). The fact that Lilly never filed a motion to dismiss on this issue speaks volumes on this issue.

In any event, it is wholly improper to refuse to produce discovery on the grounds of an affirmative defense such as preemption. *See Bruesewitz v. Wyeth LLC*, 131 S. Ct. 1068, 1087, n.2 (2011) (Federal preemption is "an affirmative defense upon which the defendants bear the burden of proof[.]"). If an affirmative defense were valid grounds to prohibit discovery, considering Lilly's forty-five defenses asserted in its answer, there would never be any discovery. I will file a motion with the Court.

<u>Matthew Kuntz</u>

Lilly identified "Matt Kuntz" as one of "the key employees or consultants who played a significant role in or [was] responsible for the creation and updates of Cymbalta's United States Physicians Package Insert[.]" See, Lilly's Response to Interrogatory No. 1. Thus, he has relevant information and should be subject to deposition. The Court ordered Lilly to produce his emails pursuant my request as outlined in my letter dated March 19, 2015. Plaintiffs plan to depose Mr. Kuntz about Cymbalta and the Cymbalta label. Please advise on the status of arranging his deposition. If you are unable to reach him, I will go ahead and subpoena him directly.

Torkil Fredborg

Torkil Fredborg played a substantial role in developing the language contained on the European Cymbalta label and engaged numerous witnesses, including Dr. Perahia, about the issue of discontinuation. Mr. Fredborg will be deposed about his understanding of the withdrawal risk of Cymbalta, his discussions with various Lilly personnel about that risk, i.e., Dr. Detke, Dr. Perahia, and Dr. Wohlreich, what information was exchanged about the reasons the European label would contain some accurate risk information and the U.S. label would not, etc. I understand Mr. Fredborg is in the U.K., but that should not pose a problem setting up and / or conducting the deposition, as was done with Dr. Perahia. Please advise whether Lilly will produce this witness or whether Plaintiffs will need to file an appropriate motion.

Antonio Crucitti

Antonio Crucitti inserted himself into the discussions about the way Lilly was warning about discontinuation both in its U.S. Product Insert and in the core data sheet. *See, e.g.*, CYM-02224535. Indeed, Dr. Crucitti was heavily involved in developing the language re. 1% or greater, and suggested that the 1% be taken out of the label altogether. *See, e.g.*, CYM-02275911. Plaintiffs want to ask Dr. Crucitti questions about his understanding of the risks of withdrawal, his views about the sufficiency of the Cymbalta label, etc. Please advise whether Lilly will produce this witness or whether Plaintiffs will need to file an appropriate motion. Also, please advise whether Lilly will produce his email correspondence pursuant to my letter dated March 19, 2015.

Virginia Wyss

Virginia Wyss appears to have been a central Lilly employee who played a significant role in make changes to the Cymbalta label and core data sheet while she was at Lilly. Questions about label wording, changes, and development of label language appeared to be routed through Ms. Wyss. Accordingly, Plaintiffs plan to depose Ms. Wyss about Cymbalta, the risks of discontinuation, her understanding of Cymbalta label, her role in its development, etc. *See, e.g.*, CYM-02279719. Please advise whether Lilly will produce this witness or whether Plaintiffs will need to file an appropriate motion. Also, please advise whether Lilly will produce her email correspondence pursuant to my letter dated March 19, 2015.

Carol Stephens

Carol Stephens played an important role in developing the language in the Cymbalta label, both proposing specific language and proposing various strategies about any warning related to, among other things, discontinuation of Cymbalta. *See, e.g.*, CYM-022275931, CYM-02363882, CYM-1912040. Ms. Stephens was involved in maintaining the language in the core data sheet and specifically worked on label discussions related to the discontinuation warning. Plaintiffs plan to depose Ms. Stephens about her knowledge of

the Cymbalta label, any changes made to the label, and her general understanding of the issue of withdrawal, among other things. Please advise whether Lilly will produce this witness or whether Plaintiffs will need to file an appropriate motion. Also, please advise whether Lilly will produce her email correspondence pursuant to my letter dated March 19, 2015.

Michael Roesner

Michael Roesner appears to be copied on many correspondence about the Cymbalta label and was evidently heavily involved in maintaining the Cymbalta warning language. During our discussion, Mr. Imbroscio stated that Mr. Roesner only worked on Cymbalta for a little over a year. In a gesture of good faith, Plaintiffs will withdraw his deposition notice provided that his emails are produced pursuant to my letter dated March 19, 2015. Plaintiffs would be fine with limiting his email production to the short period of time that he worked on Cymbalta. Please advise if Lilly will accept this compromise.

Please get back to me on these issues as soon as possible, as I would like to know, one way or the other, what PLaintffs will need to move on by COB on Wednesday at the latest, and preferably by tomorrow.

Thanks,

Brent

-----Original Message-----
From: Stekloff, Brian [mailto:BStekloff@cov.com]
Sent: Friday, April 03, 2015 2:38 PM
To: Wisner, R. Brent; Broomandan, Amber
Cc: Imbroscio, Michael; Jones, Phyllis; Reynolds, Brett
Subject: Ali and Hagan-Brown Deposition Notices

Dear Brent:

I write to follow-up on our discussion after court regarding your deposition notices in Ali and Hagan-Brown. Our positions regarding the proposed deponents are as follows:

We are prepared to produce Dr. Deske and Ms. Wohlreich on dates when the witnesses are available. We have contacted both witnesses and are in the process of determining their availability so that we can propose such dates.

With respect to the other witnesses, the status is as follows:

Mr. Roesner is a current employee. We ask that you reconsider your need to depose him, but we are obtaining his availability in the meantime.

Mr. Crucitti is a former employee whom we understand is located in Italy. We found out after court that he is now actually with GSK, which acquired the Novartis business he worked in. We'll reach out to GSK, but in the meantime, we request that you provide us with more information regarding the topics on which you seek to depose him.

Mr. Fredborg is a current employee located in the United Kingdom. We are in the process of determining his availability, but let us know if the goal in your deposition is simply to cover EU labeling issues, in which case we will need to consider whether to lodge a relevance objection.

Mr. Kuntz is a former employee who is currently working at AbbVie. We have contacted his current employer to determine his availability, but our understanding is that Mr. Kuntz is on vacation until Wednesday, April 8, 2015<x-apple-data-detectors://1>. Moreover, we request that you provide us with more information regarding the topics on which you seek to depose him in order to determine whether we will produce him.

Ms. Stephens and Ms. Wyss are former employees. We have attempted to contact both of them, but have been unable to reach them thus far. Moreover, we request that you provide us with more information regarding the topics on which you seek to depose them in order to determine whether we will produce them.

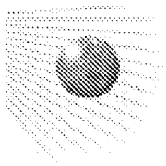
With respect to your 30(b)(6) notice, we reserve the right to object to particular subject matters described in your notice. With that understanding, we are generally prepared to produce a witness regarding one of your four topics: clinical trials. Ms. Wohlreich will testify regarding clinical trials and we ask that you complete her deposition as a fact witness and as a 30(b)(6) witness in a single day.

We will not produce a witness with respect to European labeling for Cymbalta. The European label has no bearing on your clients' claims. See In re Seroquel Prods. Liab. Litig., No. 6:06-MD-1769-ORL-22-DAB, 2009 WL 223140, at *6 (M.D. Fla. Jan. 30, 2009), aff'd, 601 F. Supp. 2d 1313 (M.D. Fla. 2009) (holding that "foreign [prescription] labels and . . . foreign regulatory actions have no relevance" in a products liability action concerning medicines and labels created according to U.S. regulatory standards); see also In re Viagra Prods. Liab. Litig., 658 F. Supp. 2d 950, 965 (D. Minn. 2009) (excluding "discussion of foreign regulatory actions [as] irrelevant"). We also will not produce a witness with respect to Lilly's marketing relationship with WebMD. Under Virginia's learned intermediary doctrine, a manufacturer's duty to warn of potential risks associated with a medication runs to the prescribing physician. See Talley v. Danek Med., Inc., 179 F.3d 154, 162-63 (4th Cir. 1999); Pfizer, Inc. v. Jones, 272 S.E.2d 43, 44-45, 221 Va. 681, 684 (1980). Absent testimony that Ms. Hagan-Brown's or Ms. Ali's prescribers relied on WebMD to determine the potential risks of Cymbalta, Lilly's alleged relationship with WedMD has no bearing on this matter. Finally, we will not produce a witness regarding the Cymbalta capsule. See PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2580-81 (2011) (holding plaintiff's state law design defect claim was preempted by federal law given FDA's role); see also Bartlett, 133 S. Ct. at 2475 (rejecting design defect claim for similar reasons); In re Celexa & Lexapro Mktg. & Sales Practices Litig., 779 F.3d 34, 35 (1st Cir. 2015); Thompson v. Allergan USA, Inc., No. 4:13CV00030 AGF, 2014 U.S. Dist. LEXIS 10081, at *13-16 (E.D. Mo. Jan. 28, 2014) (finding state-law claims preempted where plaintiffs alleged that manufacturer of prescription eye medication should have distributed medicine in vials containing smaller quantities). We are prepared to litigate these issues before the Court.

I am available at your convenience to discuss these issues.

Regards, Brian

EXHIBIT 4



Torkil Fredborg/EMA/LLY@LILLY
08/19/2008 06:27 AM

To Steve Sugino/AM/LLY@Lilly
cc
bcc
Subject 20 mg update from Sue

Steve,

I did see Sue this morning and she basically repeated all the argument you and I discussed yesterday. She agrees that one cannot totally rule out any risk, but that it would be very remote.

Ultimately, she believes that in the absence of any data, the regulatorys can not prevent us from withdrawing the application if we so wish.

Did you speak to Jim/David concerning the sentence in question?

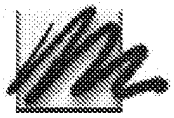
After my last revisions yesterday, the sentence now reads:
"A 30 mg formulation of duloxetine is available for the purposes of tapering treatment and is helpful for most patients where a 2 week taper is required. However, some patients might need a longer taper, and the only way that this can currently be done is via alternate day dosing. This practice carries the theoretical risk of itself inducing discontinuation symptoms in some patients due to the enforced interruption of treatment which is precisely what the taper should be designed to avoid. The availability of a 20 mg formulation would allow clinicians to reduce the dose of duloxetine more gradually at the end of treatment, where necessary – for example 60 mg to 40 mg to 30 mg to 20 mg to zero - without the need to resort to alternate day dosing."

If you want to further cut this sentence we need to be careful that it doesn't defeat the arguemtn for the introduction of a new dose. Redacted

Redacted

Best regards
Torkil

EXHIBIT 5



Carol H Stephens /AM/LLY
02/13/2007 03:23 PM

To Miyoko Shimada/AP/LLY@Lilly, Ann Robbins Sakai/AM/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, Isabelle Murray/AM/LLY@Lilly, Jens.Croenlein@bc.boehringer-ingelheim.com, Joanne Lorraine/AM/LLY@Lilly, Peter Robins/AM/LLY@Lilly, RAPGC, RCEEAMEA, RLATINAM, RUSJACAN, William G Losin/AM/LLY@Lilly, HORNS@ing.boehringer-ingelheim.com, RESPCC, Sara M Doshi/AM/LLY@Lilly, Deborah G Plessinger/AM/LLY@Lilly, Lisa Vierhile Rhein/AM/LLY@Lilly, Ailsa Jean Surman/AP/LLY@Lilly, BRECHTS@ing.boehringer-ingelheim.com, Torkil Fredborg/EMA/LLY@Lilly

cc Carol H Stephens/AM/LLY@Lilly

bcc

Subject ACTION REQUIRED: Update to duloxetine CDS approved by GPLC 31JAN07

On 31 January 2007 the Global Product Labeling Committee (GPLC) approved updates to the duloxetine Core Data Sheet.

- If you market duloxetine or have regulatory commitments with another company that markets duloxetine, labeling must be updated. Redacted Redacted
- If duloxetine is approved but not currently marketed and you desire to keep your dossier current, labeling must be updated.
- If you do not market duloxetine or do not have regulatory commitments with another company, you may delete this message.

The following changes are required. These changes must be made in all duloxetine labels (Cymbalta, Yentreve, Xeristar, and Ariclaim). The GOLDTRACK number is indicated. Additions are underlined and deletions are struck through. The GOLDTrack number is in brackets and red font.

Duloxetine

Section c.8 Addition of new terms to the discontinuation symptoms section and deletion of an out of date statement

Discontinuation symptoms have been reported when stopping duloxetine. The most commonly reported ~~S~~symptoms ~~may~~ following abrupt discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paresthesia, vomiting, irritability, ~~and~~ nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo.{41262}

~~Dizziness, nausea, and headache (≥ 5%) were also reported as common adverse events upon duloxetine discontinuation~~.

Section c.8 Addition of a new spontaneous term

Metabolism and nutrition disorders: *Very rarely (< 0.01%)* : Hyponatremia, hyperglycemia (reported especially in diabetic patients){41263}

Section c.9 Updates to the overdosage section

There is limited clinical experience with duloxetine overdose in humans. In ~~premarketing~~ clinical trials, cases of acute ingestions above ~~1400~~3000 mg, alone or in combination with other drugs, were reported with none being fatal. However, in ~~P~~post marketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as approximately 1000 mg. ~~includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone, at a dose of approximately 1000 mg.~~{41264} Signs and symptoms of overdose (most with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures.

- **Independent Labeling:** Submit the changes as soon as possible, as consistent with affiliate practice, but not later than 6 months after GOLD distributes the change to affiliates.
- **Dependent Labeling:** Submit as soon as possible, as consistent with affiliate practice, but not later than three months after approval of the labeling in the country on which your affiliate depends.
- Redacted
- US plans: will be submitted no later than August, 2007

Redacted

IMPLEMENTATION TIMELINE

The timeline for use in packaging (after regulatory approval has been obtained) is upon exhaustion, but not later than six months from time of change proposal implementation approval. You must communicate this implementation information to the manufacturing site.

1. A submission date of August 2007 will be entered into RAPT for you. Please note that you are encouraged to submit these changes as soon as possible, so adjust the planned submission date within the submission timeline appropriately. For Independent labeling, however, the changes **must** be submitted by 5 August 2007.
2. Submit the change to your regulatory authority (as required). Contact GOLD if your regulatory authority has an issue or requests additional supporting data. (To propose a labeling change, complete and send the labeling change request template to GOLD.)
3. After submitting the labeling change
   - Update GOLDTrack to "Submitted to MOH and awaiting approval" within 30 calendar days of submission.
   - Enter the submission date in RAPT and change the registration status from "planned" to "submission completed."
4. After you receive a response from your regulatory authority (approval or rejection)
   - Update GOLDTrack to "Yes" or to "Submitted to MOH and rejected" within 30 calendar days
   - Update RAPT and change the registration status

PLEASE NOTE: There will be two identical label change activities entered, one for Yentreve and one for Cymbalta. These records have been entered only for countries that have started the submission process or gained approval for Yentreve, Cymbalta or both.

Core Data Sheet in track changes

Core Data Sheet with all changes accepted

Supporting documentation

Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

EXHIBIT 6

Antonio Stefano Crucitti/EMA/LLY
01/31/2008 05:38 AM

To Mary E Nilsson/AM/LLY@Lilly
cc Beatrice Grimault/EMA/LLY@Lilly, David G Perahia/EMA/LLY@Lilly
bcc
Subject Re: EU GAD regulatory question

History: This message has been replied to.

Hi Mary,

Looking only at one study is unlikely to produce statistically significant results.
My suggestion is to look at GAD (abrupt vs taper) by dose including anything we have (i.e. for tapering I would include all 4 studies).
I would do the same for MDD (i.e. abrupt vs taper by dose).

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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Answers That Matter.

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Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
30/01/2008 22:11

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc Beatrice Grimault/EMA/LLY@Lilly, David G Perahia/EMA/LLY@Lilly
Subject Re: EU GAD regulatory question

When I was looking at the data, I was focusing on how MDD Taper compared with GAD Taper.
MDD Taper=12.7% v 17.5%
GAD Taper=16.7% v 22.2%

So, I was thinking they were quite similar - GAD a little higher but with both placebo and duloxetine.

The best way to look at GAD Taper versus GAD abrupt is Study HMBR. In the current analyses, GAD abrupt is just from 1 study (HMBR) and GAD Taper is from 4 studies (HMBR being one of them). So, if you use HMBR only, it would be a better comparison. From the HMBR CSR, Table 12.5, the numbers are: Dulox 60 abrupt=31%, Dulox 60 taper=31%, Dulox 120 abrupt=36%, Dulox 120 taper=24%. The statistical tests looked to be insignificant. Numerically, the 120 abrupt versus 120 taper looks different.

HMCB is a MDD study that has both abrupt and taper. It appears that study has an abbreviated report

only, so I'm not finding a table on taper-emergent events. I did find a program but not the output. I'll continue to work on this if necessary. Maybe there's a manuscript on this.

I guess the main question is whether GAD should be tapered differently than MDD. My understanding is that the SPC still says to taper for MDD despite the data.
Anyway, let's discuss this some more.....

By the way - the ouptut below is still in TEST. I will let you know when validation is completed.

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Antonio Stefano Crucitti/EMA/LLY

Antonio Stefano Crucitti/EMA/LLY
01/30/2008 07:23 AM

To David G Perahia/EMA/LLY@Lilly
cc Mary E Nilsson/AM/LLY@Lilly, Beatrice Grimault/EMA/LLY@Lilly
Subject Re: EU GAD regulatory question

Hi David,

Mary provided me with the tables on withdrawal symtpoms in MDD and GAD (abrupt and taper).
My interpretation of these data is that tapering appears much more beneficial in GAD patients than in MDD patients. In fact, in GAD patients treated with placebo, the % of all DEAEs does not change (16.7% tapering disc. vs. 16.2% abrupting disc.) but in duloxetine treated patients the difference is clear (22.2% tapering vs. 33.3% abrupting). Therefore, our position that tapering vs. abrupting is basically the same does not seem applicable in GAD patients.
In MDD patients, abrupting is associated with a higher (twice) frequency of DEAEs in both duloxetine and placebo.

In summary, based on these data I think we should provide a proposal for tapering in GAD patients in the SPC (as requested).

What is your interpretation ?

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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Answers That Matter.

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unauthorized amendment, tampering and viruses, and we only send and receive e-mails on the basis that we are not liable for any such corruption, interception, amendment, tampering or viruses or any consequences thereof.

Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
29/01/2008 15:31

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Antonio - I believe this is what we want for the new EU GAD question regarding tapering in GAD versus MDD.
I believe we only need the 2 reports addressing tapering and not the 2 reports addressing abrupt discontinuation.
Thoughts?

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Wei J Chen/AM/LLY

Wei J Chen /AM/LLY
01/28/2008 04:56 PM

To Mary E Nilsson/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Hi, Mary,

attached are the outputs in testing, they are not been p.reviewed yet. just want to let you take a look first to see if these reports cover what you want to see. I will double check program (which was started from scratch) logic tomorrow.

[attachment "fqaesc14.doc" deleted by Mary E Nilsson/AM/LLY] [attachment "fqaesc11.doc" deleted by Mary E Nilsson/AM/LLY] [attachment "fqaesc12.doc" deleted by Mary E Nilsson/AM/LLY] [attachment "fqaesc13.doc" deleted by Mary E Nilsson/AM/LLY]

Wei J Chen
433-1469

Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY

01/25/2008 04:38 PM

To Wei J Chen/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Looks like it makes sense to move forward with MDD and GAD - studies with taper. I guess we may not have a good starting program though?

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Wei J Chen/AM/LLY

Wei J Chen/AM/LLY
01/25/2008 04:18 PM

To Mary E Nilsson/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Hi, Mary,

From what I know about the past studies, it seems like simply rerun the two programs (RMP.F1JSSAFE.SASPGM(FQAESWA2, FQAESYA4)) for MDD and GAD may not work. Reason for saying this is: I have some total counts of patients who entered taper/abrupt phases from Q405 GAD submission, and the total N for each treatment group for taper are way less than FQAESWA2. The only difference of GAD/MDD placebo-controlled studies between Q405(used for GAD sub) and Q207(used for EU GAD) are two studies HMDH, HMDW and the counts from these two studies could not explain the big difference at all. I do suspect the two programs need to be revised.

Anyway, following are what I found for MDD / GAD studies with taper:
HMBR, HMDT, HMDU, HMDW, HMCB, HMBV, HMDH

MDD / GAD studies with abrupt:
HMBR, HMAG, HMAQA, HMAQB, HMATA, HMATB, HMBHA, HMBHB, HMCB, HQAC, HMAH, HMAI, HMAYA, HMAYB

note: both studies HMBR, HMCB had some patients into taper, and some other into abrupt.

Let me know if this is consistent with what you have, also let me know if you want me to dig more into the two programs or you want to wait till Steve gets back.

Wei J Chen
433-1469

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
01/25/2008 02:06 PM

To Wei J Chen/AM/LLY@Lilly
cc
Subject EU GAD regulatory question

Wei,
Here's the question from the EU:

1. The MAH should provide comparative data on the withdrawal signs when the treatment is stopped in GAD as compared to those observed in the depression indication (frequency, nature of events, effect of tapering). The MAH should provide a proposal of tapering that may be applied in the SPC, if different when compared to the depression indication.

So, we want analyses of GAD and analyses of MDD. Our GPS folks will visually compare those.
Here's what I found:

RMP.F1JSSAFE.SASPGM(FQAESWA2) - All placebo-controlled, DEAE for patients who tapered off drug
RMP.F1JSSAFE.SASPGM(FQAESYA4) - All placebo-controlled, DEAE for patients who abruptly stopped drug

RMP.F1JSFMSS.SASPGM(FQAESG5) - GAD - DEAE for patients who tapered or abruptly stopped
RMP.F1JSFMSS.SASPGM(FQAESF0) - All placebo-controlled - DEAE for patients who tapered off drug (appears to be the same as FQAESWA2)

I believe what we need is either FQAESWA2 or FQAESF0 run for GAD only and MDD only.
Also, FQAESYA4 run for GAD only and MDD only.

Looks like GAD has a study (HMBR) that compares taper vs abrupt. That may come into the response, but nothing new would need to be run.
Let me know if you have any questions! Thanks!

_____
Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

_____

Carrie A Krueger/AM/LLY

Carrie A Krueger /AM/LLY
01/07/2008 02:02 PM

To Antonio Stefano Crucitti/EMA/LLY@Lilly, Cynthia Hallberg/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Mary E Nilsson/AM/LLY@Lilly, Melissa Elizabeth Spann/AM/LLY@LILLY, Torkil Fredborg/EMA/LLY@Lilly
cc Diane Mackleston/EMA/LLY@Lilly, James M Russell/AM/LLY@Lilly, Nayan Acharya/AM/LLY@Lilly
Subject GAD Preliminary Response Timeline

Team,
I will be providing project management support for the GAD responses due to EMEA on Feb. 22nd. After discussions with Beatrice, we have created the following timeline for the preliminary and subsequent final responses:

This week - Cynthia to launch shell, begin draft and route to team, analyses work, follow up on action items, Beatrice to talk with Antonio re: safety questions
Monday, Jan. 14th @ 9-10:00 a.m. - next working group meeting
Week of Jan. 14th - proposed analyses to be completed
Jan. 21 - draft preliminary responses complete; consolidated assessment report due to Lilly
Jan. 22-Feb. 8 - review final questions, determine if further analyses needed, formulate final responses
Feb. 11-12 - QC and editorial review, finalize response document
Feb. 13 - sign off/approval
Feb. 14 - to publishing
Feb. 21 - submit to EMEA

Please let me know if you have any questions.

Carrie Krueger
Project Management Associate Consultant, NS Brand Stewardship
317-651-8298 (phone)
317-276-5064 (fax)
kruegercn@lilly.com

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EXHIBIT 7

James L Gahimer/AM/LLY@LILLY
12/14/2006 11:31 AM

To Alena R Gipson/AM/LLY@Lilly, Alberto Lledo/EMA/LLY@Lilly, Antonio Stefano Crucitti/EMA/LLY@Lilly, Natalie DiPietro/AM/LLY@Lilly, Nayan Acharya/AM/LLY@Lilly
cc Saleel J Kulkarni/AM/LLY@Lilly
bcc
Subject Re: Fw: drug withdrawal reaction

All,

Thank you for making me aware of this case and the concerns regarding coding.
Upon re-review of the case, I agree with Stefano that drug withdrawal reaction should be coded. It would clearly make the case
easier to identify. I will discuss this additional event term with Sal. Regarding follow-up, we have sent a suicide follow up form
and are inquiring about any other symptoms associated with the sudden discontinuation, the timing of the symptoms and if duloxetine was reinitiated
and what was the effect on any potential withdrawal symptoms.

Thanks again,

Jim

Alena R Gipson/AM/LLY

Alena R Gipson /AM/LLY
12/14/2006 07:04 AM

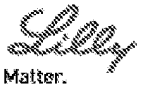
To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc Alberto Lledo/EMA/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Natalie DiPietro/AM/LLY@Lilly, Nayan Acharya/AM/LLY@Lilly
Subject Re: Fw: drug withdrawal reaction

Dear Antonio,

I would be more than happy to follow-up with the US case manager, More than likely a request for follow-up information may have been forwarded to the reporting physician...but will confirm.

Will keep you posted.
Thank you,
Kind regards, Alena

Alena R. Gipson, Case Management Associate GPS-Central
Global Product Safety
Eli Lilly and Company
Lilly Corporate Center, DC 2542
Indianapolis, IN 46285
www.lilly.com
Tel: 317-651-9117 Fax: 317-651-7434



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Antonio Stefano Crucitti/EMA/LLY

Antonio Stefano Crucitti/EMA/LLY
12/14/2006 05:57 AM

To Alena R Gipson/AM/LLY@Lilly
cc Nayan Acharya/AM/LLY@Lilly, Alberto Lledo/EMA/LLY@Lilly, Natalie DiPietro/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly
Subject Re: Fw: drug withdrawal reaction

Dear Alena,

I completely agree that it is a physician's call to decide whether the event drug discontinuation symptom should be coded or not. My concern it that I cannot see any comment or administrative note in ARGUS regarding this assessment. Cases like this should not be confounded with cases occurring while on treatment, provided that there is sufficient information for a medical assessment. Therefore, in my opinion the company physician's assessment should be included in ARGUS. If no assessment can be provided, we should ask the reporting physician to provide us with an assessment. Could you please follow-up this case ?

Kind regards
Antonio

Antonio Crucitti - Safety Physician, Global Product Safety, Neuroscience

---

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Alena R Gipson/AM/LLY

Alena R Gipson /AM/LLY
14/12/2006 02:21

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc
Subject Re: Fw: drug withdrawal reaction

Dear Antonio,

Hope you are doing well. Natalie and I discussed the case referenced below US200610004443 and

really felt that after reading the RQS document regarding drug withdrawl reactions it really is the physician's call to code the event drug withdrawal in this case.:

From the RQS for Adverse Event Coding: Only use the event term "drug withdrawal" for adverse events (signs/symptoms) that have been reported to be the direct result of drug discontinuation.

From the case: On an unknown date, duloxetine was abruptly stopped, and the patient experienced feelings of sadness and thoughts of suicide, and was admitted to the inpatient unit.

Since this is a US case, it maybe helpful to discuss further with Jim Gahimer. A case manager in the US affiliate may be able to update this case.
Thank-you,
Kind regards, Alena

Alena R. Gipson, Case Management Associate GPS-Central
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Answers That Matter.

Natalie DiPietro/AM/LLY

Natalie DiPietro /AM/LLY
12/01/2006 12:52 PM

To Alena R Gipson/AM/LLY@Lilly
cc Alberto Lledo/EMA/LLY@Lilly, Nayan Acharya/AM/LLY@Lilly, Antonio Stefano Crucitti/EMA/LLY@Lilly, David Appiah-Badu/EMA/LLY@Lilly, Timothy M Conrad/AM/LLY@Lilly, Danielle M Klinger/AM/LLY@LILLY
Subject Fw: drug withdrawal reaction

Hi Lena,
Please see below - we discussed this at our surveillance meeting this week - please take a look & stop by my desk when you have a chance and I'll fill you in on our discussion at the meeting.
Thanks,
Natalie
Antonio Stefano Crucitti/EMA/LLY

Antonio Stefano Crucitti/EMA/LLY
11/22/2006 06:45 AM

To Nayan Acharya/AM/LLY@Lilly, Alberto Lledo/EMA/LLY@Lilly, Natalie DiPietro/AM/LLY@Lilly
cc
Subject drug withdrawal reaction

FYI,

A case of suicide ideation following abrupt discontinuation of duloxetine.
Natalie, for our discussion at the next bi-weekly meeting: this case is neither ticked as drug withdrawal reaction nor the drug withdrawal reaction is coded as an event term. Is there any other way to retrieve a case like this if we need to perform a review of the discontinuation-related reactions received from the spontaneous reporting system ? If the answer is no, we need to find a solution. My personal opinion is that even if the term withdrawal reaction is not mentioned as such by the reporting physician, I think that we may add an additional term (or tick the case) based on our medical judgment.

[attachment "US200610004443.pdf" deleted by Alena R Gipson/AM/LLY]

Antonio Crucitti - Safety Physician, Global Product Safety, Neuroscience

---

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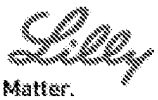

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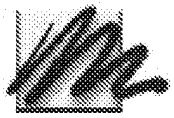
EXHIBIT 8

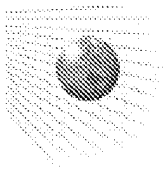


Carol H Stephens /AM/LLY
08/16/2006 02:21 PM

To Nayan Acharya/AM/LLY@Lilly
cc
bcc
Subject Fw: Criteria for Events Selection for CDS and USPI

Nayan -- this is a good summary.
Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

----- Forwarded by Carol H Stephens/AM/LLY on 08/16/2006 02:21 PM -----



Fujun Wang /AM/LLY
07/07/2006 02:51 PM

To Ann Robbins Sakai/AM/LLY@Lilly
cc Alberto Lledo/EMA/LLY@Lilly, Carol H Stephens/AM/LLY@Lilly, Doug Williamson/AM/LLY@Lilly, Eric David Johnson/AM/LLY@Lilly, Matt Eggers/AM/LLY@Lilly, Maurice Lunik/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly
Subject Criteria for Events Selection for CDS and USPI

Team:

It sounds like some people are not very clear on how the events in the CDS and USPI were selected. Here I'd like to summarize the criteria for both doucments and point out the differences so that we can make decisions on the event seclection criteria for the PLR.

1. Event selection criteria for the TEAE table in the USPI.

For each indication, "the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of [Indication] placebo-controlled trials and with an incidence greater than placebo".

Please note, only registration studies were included for the AE tables in USPI.

2. Event selection criteria for the TEAE in the Core Data Sheet (CDS).

Categories for Treatment-emergent Adverse Events (TEAE) and Discontinuation-emergent Adverse Events (DEAE)

A. Statistically significant difference in incidence compared with placebo AND incidence for duloxetine > that for placebo.

B. Duloxetine incidence rate twice the placebo incidence rate, although the difference was not statistically significant.

C. Incidence rate with duloxetine ≥ 10%.

To Determine Inclusion/Exclusion of Events

After all events are categorized according to the algorithm criteria defined above, use the following rules to include/exclude events in the Core Data Sheet:

1. *If the event hits 2 or more criterion, include it in the Core Data Sheet.*
   OR
2. *If the event hits only 1 criteria, use clinical judgement to determine inclusion/exclusion.*

For each indication and overall, we apply the above algorithm. If any of the event meets the inclusion criteria for any one indication or overall, then that event will be included in the CDS. I attached the CDS algorithm document here also.

Core Data Sheet Algorithm 2006-Feb-7.doc

3. Potential problems for the PLR

We can see that the event selection criteria for CDS and USPI are different , we need to decide what criteria we want to apply for PLR. It sounds like we are following the CDS criteria , then do we apply the criteria by indication or only apply the criteria for the overall for the purpose of PLR ? Do we have to keep PLR be consistent with CDS ? We need to evaluate the consequences no matter what criteria will be applied .

This is an important decision before we can move forward . We can discuss the criteria in next week 's meeting,

Fujun

EXHIBIT 9

Carole Boylan /AM/LLY
11/06/2008 03:09 PM

To Jill C Chappell/AM/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly, Evelyn Lobo/AM/LLY@Lilly, Linette M Ortiz-Moore/AM/LLY@Lilly, Lynette Timmons/AM/LLY@Lilly, Mary Pat Knadler/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly
bcc
Subject Re: Duloxetine - warfarin study HMFP

History: This message has been replied to.

Hi Jill,

If the US agrees to this revision, we would also have GPS and Bryan weigh in on the appropriate timing in addition to looking at our planned labeling activity. Mid-December might be a good target for submission given how early in the process we are. If the change is limited to the Drug Interactions Section then this would likely be considered a CBE (Bryan to confirm) where we would implement the change into the label following submission to FDA.

I've summarized below the approximate dates for current planned labeling activities for Cymbalta USPI in 2008: If we submit HMFP label change, it would likely be a separate submission activity. Given the level of submission activities, we should be able to coordinate the printing portion to minimize impact on printed pieces while ensuring we are getting this information in the labeling in the appropriate timeframe.

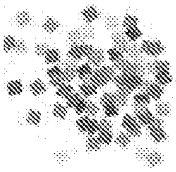
20 Nov 2008 GAD MoE Prior Approval Supplement
15 Dec 2008 PSUR08 Adverse Reactions CBE
15 Dec 2008 Med Guide revisions

In summary, here are the tasks that need to be completed before we submit this change to US
1. Confirm no CDS change warrented
2. Confirm with US the need for revising USPI
3. Develop labeling proposal
4. Confirm proposal with key stakeholders
5. Send USPI for internal Review and Approval (sign-off)
6. Submit to Agency

thanks, let me know if you need any addl info - carole

Assoc. Labeling Consultant
Global Regulatory Affairs - GOLD
Cymbalta
317-276-9056
317-433-6771(fax)

Jill C Chappell/AM/LLY



Jill C Chappell /AM/LLY
11/06/2008 01:48 PM

To Carole Boylan/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly, Evelyn Lobo/AM/LLY@Lilly, Mary Pat Knadler/AM/LLY@Lilly, Lynette Timmons/AM/LLY@Lilly, Linette M Ortiz-Moore/AM/LLY@Lilly
Subject Re: Duloxetine - warfarin study HMFP

Carole,
Thanks for the information. I have checked with our biopharm team and we agree that a change to the CDS is probably not warranted since warfarin is not the only anticoagulant used globally, but do recommend revisions to relevant local labels based on HMFP, in particular the USPI and SPC. For the USPI, I will summarize our recommendations and discuss with Michael Robinson and Antonio as you suggest, but would appreciate your input on what would be the appropriate timing based on any other label revisions.

Torkil - In a previous email (pasted below for others' behalf), you already stated an intention to amend a sentence in the SPC. Please, can you advise on the possible timing of this revision?

> The CSR has been submittee in the EU - we have not formally proposed an SPC change, but the intentiion is to amend the second sentence of the following paragraph in line with the study results. I believe that sentence is off core in the first place.
>
> *Anticoagulants and antiplatelet agents:* Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

Thanks!
Jill

Carole Boylan/AM/LLY

Carole Boylan /AM/LLY
11/04/2008 12:23 PM

To Jill C Chappell/AM/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly
Subject Re: Duloxetine - warfarin study HMFP

Hi Jill.

Thanks for your comments. I think the next step would be to confirm with global medical and/or GPS whether this data would impact the CDS. Then for the US side, depending on the nature of the data (safety vs efficacy), we would then need to confirm with the team, i.e., US medical (M. Robinson) and/or GPS (Antonio) whether the current USPI needs to be revised, and the most appropriate location for the data, (7 DRUG INTERACTIONS, 12 CLINICAL PHARMACOLOGY, etc). We should also think about our timelines and try to coordinate this potential change with other ongoing labeling activities and impact on printed pieces as appropriate, I can help with that.

Can you have the discussions to confirm if a revision to labeling is required? I can provide labeling support to help. If the team decides to revise labeling, I can work with you to develop draft labeling and facilitate.

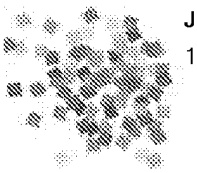
Attached is a document which contains the CDS and USPI text for Drug interactions and Clinical Pharmacology sections for your reference. Let me know if I can help.

Drug Interaction_CDS_USPI.doc

thanks, carole

Carole Boylan
Assoc. Labeling Consultant
Global Regulatory Affairs - GOLD
Cymbalta
317-276-9056
317-433-6771(fax)

Jill C Chappell/AM/LLY



Jill C Chappell /AM/LLY
10/29/2008 10:48 AM

To Carole Boylan/AM/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly, "Mr. Torkil Fredborg" <FREDBORG_TORKIL@LILLY.COM>, Evelyn Lobo/AM/LLY@Lilly, Mary Pat Knadler/AM/LLY@Lilly
Subject Re: Duloxetine - warfarin study HMFP

Hi Carole,
I was the lead CP for this study (as CRS). I was wondering if the results of the study should be included in Section 7, as well as a few minor clarifications - for example Section 7.10 we could update since S-warfarin is a 2C9 substrate.

Evelyn Lobo is our PK scientist and Mary Pat Knadler is our ADME scientist.

Thanks,
Jill

~~*~*~*~*~*~*~*~*~*~*~*

Jill C. Chappell, Pharm.D.
Assoc. Clinical Research Scientist
Global EPM - Biopharmaceutics
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 651-6268
chappelljc@lilly.com
Carole Boylan/AM/LLY

Carole Boylan /AM/LLY
10/27/2008 10:38 PM

To Bryan E Boggs/AM/LLY@Lilly, Jill C Chappell/AM/LLY@Lilly
cc "Mr. Torkil Fredborg" <FREDBORG_TORKIL@LILLY.COM>
Subject Re: Duloxetine - warfarin study HMFP

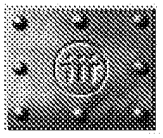
Hi Jill,

Thanks for the forward - like Bryan, I am not aware of any changes to CDS or USPI. In fact I seem to recall some correspondence in the past stating this data would not result in a label change, but as of now, I have been unable to locate that in my email. If you can tell me who was lead physician and or PK/PD

contact on HMFP, and I can followup and confirm. Thanks Carole

Carole Boylan
Assoc. Labeling Consultant
Global Regulatory Affairs - GOLD
Cymbalta
317-276-9056
317-433-6771(fax)

Bryan E Boggs/AM/LLY



Bryan E Boggs /AM/LLY
10/27/2008 03:49 PM

To Jill C Chappell/AM/LLY@Lilly, Carole Boylan/AM/LLY@Lilly, "Mr. Torkil Fredborg" <FREDBORG_TORKIL@LILLY.COM>
cc
Subject Re: Duloxetine - warfarin study HMFP

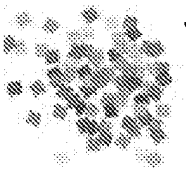
Jill, I am not aware of any USPI changes possible, but there are SPC changes proposed in Europe.
Bryan /317-681-4997/via BlackBerry.

Jill C Chappell
----- Original Message -----

From: Jill C Chappell
Sent: 10/27/2008 01:53 PM EDT
To: Carole Boylan
Cc: Bryan Boggs
Subject: Re: Duloxetine - warfarin study HMFP

Carole - sorry I didn't get you cc'd on the first message below.
Thanks,
Jill

Jill C Chappell/AM/LLY



Jill C Chappell /AM/LLY
10/27/2008 01:30 PM

To Bryan E Boggs/AM/LLY
cc
Subject Duloxetine - warfarin study HMFP

Hi Bryan,
As you probably know, we recently completed our dulox-warfarin interaction study HMFP. I was wondering if there will be any label changes based on the new results, and if so, when these changes might be made?
Thanks,
Jill

~~*~*~*~*~*~*~*~*~*~*~*

Jill C. Chappell, Pharm.D.
Assoc. Clinical Research Scientist

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Eli Lilly and Company
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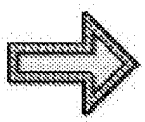
EXHIBIT 10



Michael J Robinson /AM/LLY
12/12/2007 01:38 PM

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly
bcc
Subject Re: End-of-Year vacation time

History: This message has been replied to.

Antonio.

I was double checking the slides we reviewed over the phone this week - particularly this statement:

Tinnitus upon treatment discontinuation (included in CDS dated 24 October 2007)

Here is the section on discontinuation of Cymbalta in the current USPI

USPI language:

5.6 Discontinuation of Treatment with Cymbalta

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: **dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo .**
.....

Since I don't see tinnitus mentioned - was this update part of the recent USPI update, or will we see this with the next update?

Michael

Michael J. Robinson, MD, FRCPC, FAPM
Medical Advisor
Eli Lilly and Company,
Mail Code 4103
Indianapolis, IN 46285
tel: 317-651-1138
mobile: 317-997-1912
fax: 317-651-6269

Augusta L. Robinson
USMD, Neuroscience
Administrative Assistant
Lilly Technology Center-South
Indianapolis, IN 46285
Drop Code 4103
Phone: 317-651-7386
Fax: 317-651-6269
alrobinson@lilly.com

EXHIBIT 11

Fujun Wang /AM/LLY
01/12/2006 02:26 PM

To Virginia L Wyss/AM/LLY@Lilly
cc Benjamin T Rotz/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly
bcc
Subject Re: Fw: PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)

History: This message has been replied to.

To finish my action item, here are the numbers we agreed to provide in the Label, I also attached the original report where these numbers were obtained:

For Cymbalta:

In clinical trials adverse events seen on treatment discontinuation occurred in approximately 44.8% of patients treated with duloxetine and 22.6% of patients taking placebo.

Note: The cut-off date for these data is October 1, 2004. The same table was used in Core Data Sheet.

For Yentreve:

In clinical trials adverse events seen on treatment discontinuation occurred in approximately 43.9% of patients treated with duloxetine and 23.8% of patients taking placebo.

Note: These numbers are from SBBR study only(PLA/PLA arm and 40BID/PLA arm). There are some abrupt discontinuation data in previous Yentreve studies, but the treatment doses were 40 or 20, instead of the suggested dose of 80mg. These early low dose studies were not included in the Core Data Sheet.

Fujun

fqAESC1A.doc FQAESC4F.doc

Virginia L Wyss/AM/LLY

Virginia L Wyss /AM/LLY
01/12/2006 10:01 AM

To Torkil Fredborg/EMA/LLY@Lilly, Fujun Wang/AM/LLY@Lilly, Benjamin T Rotz/AM/LLY@Lilly
cc Michael Detke/AM/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly
Subject Re: Fw: PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)

Torkil....no problem- it has happened to me before! Just please be sure to copy me on the updated list of changes! Please call me Friday morning so we can discuss Assessment report for PSUR1 and get that rolling

Here are the actions I captured.....

Torkil
send group updated table regarding sections: can we have this by Friday? except section 4.5, which will depend on Ben)
4.4: change title, compare effexor label- use of drug relatedness for hr and bp, akathesia (class labeling then dulox specific info)
4.5: warfarin, get info from Ben/Mike/Nayan regarding list of Cyp2D6 with narrow Tx index and sig safety signals
4.8: class specific, consider "common" vs "may include"

Fujun
4.4: product specific numbers, abrupt discontinuation only

Ben
4.5: get clarity on list of Cyp2D6 with narrow Tx index and sig safety signals with Mike and Nayan, Peter if needed, see IU Website, get manuscript from Peter
write justifications for pushbacks and get signoff for submission by Feb 17
send Ginny mini-milestones (first draft, final comments due, signoff, send to affiliate)

Kind Regards, Ginny

Ginny Wyss, CCRA
Associate Consultant, Pharmaceutical Project Management
Du/Flu Product Team
office 317-276-9565
cell 765-346-2158

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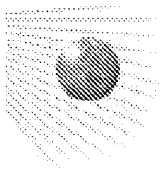
Torkil Fredborg/EMA/LLY



Torkil Fredborg /EMA/LLY
01/11/2006 04:52 PM

To Virginia L Wyss/AM/LLY@Lilly
cc
Subject Re: Fw: PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)

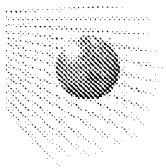
Dear Ginny,

Thanks for a good meeting today. It went pretty well and I think Ben now has a good basis for doing his writing job.. I am very sorry that you didn't get the email we sent out Friday as promised, but the good thing is that everybody else did :)
Please see below.

Again - sorry for the confusion.

Torkil
Torkil Fredborg/EMA/LLY

Torkil Fredborg /EMA/LLY



06/01/2006 17:57

To Anthony Beardsworth/EMA/LLY@Lilly, Beatrice Grimault NONLILLY/EMA/LLY@Lilly, Benjamin T Rotz/AM/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, David G Perahia/EMA/LLY@Lilly, Fujun Wang/AM/LLY@Lilly, Galen Alexander Rudolph/AM/LLY@Lilly, JENS.CROENLEIN@BC.BOEHRINGER-INGELHEIM.COM, Joachim Wernicke/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly, Brian Regele/AM/LLY@Lilly, Diane Mackleston/EMA/LLY@Lilly, Eric Baclet/AM/LLY@Lilly, Mathias.Knecht@ing.boehringer-ingelheim.com

cc D Mark Gapinski/AM/LLY@Lilly

Subject Fw: PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)

Dear all,

Please find attached the pre-read for the meeting on Wednesday, January 11th. Beatrice has compiled a very nice tabular overview of all the labeling changes we will propose in the upcoming variation.
[attachment "List of changes needed to be implemented.doc" deleted by Torkil Fredborg/EMA/LLY]

These come from three sources: CDS update in November, CDS update in December and the CHMP assessment of PSUR2, as clearly marked in the table.
The list is rather long, but we have tried to identify clearly in the comments column what needs to be discussed. Most of the CDS changes have already been revied by the group (both the CDS wording and the implementation in the SPC, so they are just mentioned here for completeness. The aim being that when we have gone through the table and clarified all action points, this will be the reference document on which the Clinical Overview for the variation produced.
To facilitate the discussion we present first the CDS changes/PSUR comments, then the draft proposed SPC wording, then any comments from our side and the last column is reserved for recording the actions agreed in the meeting.

Meeting's Purpose and desired outcomes :

1. SPC related changes: Discuss and agree on proposed SPC wording or agree on line of arguments for any counterproposals.
2. Discuss and agree the timeline and ressources for writing the Clinical Overview Addendum and availability of supporting documentation in the light of the questions on the most recent variation.

Deadline for submisison of the Type II variation is February 17th 2006.

Kind regards
Torkil

----- Forwarded by Torkil Fredborg/EMA/LLY on 06/01/2006 17:42 -----

Virginia L Wyss /AM/LLY

05/01/2006 21:17

To Anthony Beardsworth/EMA/LLY@Lilly, Beatrice Grimault NONLILLY/EMA/LLY@Lilly, Benjamin T Rotz/AM/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, David G Perahia/EMA/LLY@Lilly, Fujun Wang/AM/LLY@Lilly, Galen Alexander Rudolph/AM/LLY@Lilly,

JENS.CROENLEIN@BC.BOEHRINGER-INGELHEIM.COM, Joachim Wernicke/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly, Brian Regele/AM/LLY@Lilly, Diane Mackleston/EMA/LLY@Lilly, Eric Baclet/AM/LLY@Lilly, Mathias.Knecht@ing.boehringer-ingelheim.com

cc D Mark Gapinski/AM/LLY@Lilly

Subject Re: PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)

Dear Colleagues,

You were invited to this meeting per the request of Torkil, and your timely input is valuable to this process. Additionally, decisions from this meeting will be included in the upcoming Development Subcommittee Meeting. Pre-reads should be provided by Torkil on Friday January 6. If you cannot attend the meeting, please review the documents and network your comments through another invited individual.

Kind Regards,

Ginny

Ginny Wyss, CCRA
Associate Consultant, Pharmaceutical Project Management
Du/Flu Product Team
office 317-276-9565
cell 765-346-2158

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Calendar Entry

Calendar Entry
Meeting

☒ Notify me ☐ Mark Private ☐ Pencil In

Subject	PRIORITY: EU Label Variation (changes to PSUR2 & 2 CDS changes)
Chair	Virginia L Wyss/AM/LLY
Location	#520-2-P02

When			
	Starts	Wed 01/11/2006	11:00 AM
			1 hr 30 mins
	Ends	Wed 01/11/2006	12:30 PM
	☐ Specify a different time zone		

Where		
	Reserved	The following have been requested
	Rooms	#520-2-P02/US-Faris@lilly

Invitees		
	Invited	The following invitees have been invited
	Required (to)	Anthony Beardsworth/EMA/LLY@Lilly, Beatrice Grimault NONLILLY/EMA/LLY@Lilly, Benjamin T Rotz/AM/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, David G Perahia/EMA/LLY@Lilly, Fujun Wang/AM/LLY@Lilly, Galen Alexander Rudolph/AM/LLY@Lilly, JENS.CROENLEIN@BC.BOEHRINGER-INGELHEIM.COM, Joachim Wernicke/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly
	Optional (cc)	Brian Regele/AM/LLY@Lilly, Diane Mackleston/EMA/LLY@Lilly, Eric Baclet/AM/LLY@Lilly, Mathias.Knecht@ing.boehringer-ingelheim.com

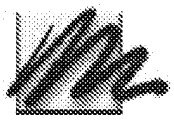
Categorize	

Description

Conference Call Numbers :
Toll Free Dial In Number: (866) 213-2145
Int'l Access/Caller Paid Dial In Number: (609) 454-9913
Access Code: 3393973

Your Notes

EXHIBIT 12



Carol H Stephens/AM/LLY@LILLY
11/01/2006 06:03 PM

To Lisa Vierhile, Ann Robbins Sakai/AM/LLY@Lilly
cc
bcc
Subject Fw: Responding to request to Beth Pangallo

FYI. .
Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

----- Forwarded by Carol H Stephens/AM/LLY on 11/01/2006 05:02 PM -----

Carol H Stephens /AM/LLY
11/01/2006 05:01 PM

To Alberto Lledo/EMA/LLY@Lilly
cc Nayan Acharya/AM/LLY@Lilly, Carol H Stephens/AM/LLY@Lilly
Subject Responding to request to Beth Pangallo

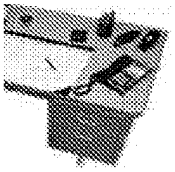
Alberto -- Beth got your voice mail on her cell phone while driving home. She doesn't have access to the data at home and asked me to respond.

Here is the key information:

- The current statement in the CDS attached is basically the same as that is in the current USPI. Both the USPI and the CDS use a 2% cut off. The statement is "Discontinuation symptoms have been reported when stopping duloxetine. Symptoms may include dizziness, nausea, headache, paresthesia, vomiting, irritability and nightmares."
- The Perehia article which was the supporting documentation for the CDS statement added in June of 2006 uses a 2% cut off.
- The listing that Beth sent you uses a 1% cut off. If you apply a 2% cut off to Beth's list, the terms would be these: dizziness, headache, nausea, insomnia, and diarrhoea as I read the listing.
- Beth and several others have indicated that the neuroscience stewardship team was supposed to make a decision on the % cut off and it is unclear whether this has happened yet.

Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

EXHIBIT 13



Ann Robbins Sakai /AM/LLY
09/11/2007 05:49 PM

To Torkil Fredborg/EMA/LLY@Lilly
cc Lisa Vierhile Rhein/AM/LLY@Lilly
bcc
Subject Re: AW: Re: GSDC Meeting

Torkil
As we discussed, just to have 'in your back pocket' and way more details than you need, this slide set summarizes all of the recent and upcoming USPI changes.
I can't remember what JEAC stands for but its the acronym Lilly uses for their partnership meetings with Quintiles, who help sale Cymbalta in the U.S.
Ann

JEAC Regulatory Update.5 sept 2007.ppt

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

EXHIBIT 14

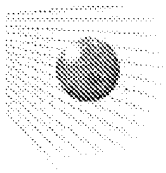
Carole Boylan/AM/LLY@LILLY
09/09/2009 08:30 AM

To Torkil Fredborg/EMA/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly, Claire Farrand/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Jeanette S Deem/AM/LLY@Lilly, Peter Robins/AM/LLY@Lilly, Stephanie de Bono/EMA/LLY@Lilly
bcc
Subject Re:URGENT: Review Requested by eob today :Japan MDD response:

Hi Torkil, thanks - I agree - SPC is aligned with CDS on discontinuation symptoms and I have made that change in the document. Carole

Carole Boylan
Assoc. Labeling Consultant
Global Regulatory Affairs - GOLD
Cymbalta
317-276-9056
317-433-6771(fax)

Torkil Fredborg/EMA/LLY



Torkil Fredborg /EMA/LLY
09/08/2009 06:12 PM

To Carole Boylan/AM/LLY@Lilly
cc Bryan E Boggs/AM/LLY@Lilly, Claire Farrand/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Jeanette S Deem/AM/LLY@Lilly, Peter Robins/AM/LLY@Lilly, Stephanie de Bono/EMA/LLY@Lilly
Subject Re:URGENT: Review Requested by eob today :Japan MDD response:

Carole,

It looks good to me except for the comment about discontinuaiton. The AE's are infact listed in the SPC, but in Seciton 4.8. (Discontinuation symptoms are mentioned three times thoughout the SPC...)

Section 4.8 wording:

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), fatigue, agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Carole Boylan/AM/LLY

Carole Boylan /AM/LLY
08/09/2009 17:33

To Bryan E Boggs/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly, Jeanette S Deem/AM/LLY@Lilly, Peter Robins/AM/LLY@Lilly
cc David G Perahia/EMA/LLY@Lilly, Stephanie de

Bono/EMA/LLY@Lilly, Claire Farrand/AM/LLY@LILLY
Subject Re:URGENT: Review Requested by eob today :Japan MDD response:

Hi Bryan, Pete and Torkil,

Nao has requested that the USPI/SPC vs CDS + rationale documents that we worked together on earllier last week, be submitted to PMDA. **Before that can happen I need to have you review these documents (by eob today 9/8) and determine if this content is accurate and acceptable (from a reg rationale standpoint) for submission to PMDA .** After you review and provide comment I will then forward these to Jim for approval (anyone else?). It is my understanding that if any addionale reg response is developed that may include information from these 2 documents would also have team review prior to submission to PMDA.

Torkil if you can't look at this could Stephanie provide review? thanks

[attachment "Japan request_SmPC_24AUG2009v1.docx" deleted by Torkil Fredborg/EMA/LLY]
[attachment "Japan request_USPI_24AUG2009.docx" deleted by Torkil Fredborg/EMA/LLY] Carole

Carole Boylan
Assoc. Labeling Consultant
Global Regulatory Affairs - GOLD
Cymbalta
317-276-9056
317-433-6771(fax)

EXHIBIT 15

Antonio Stefano Crucitti/EMA/LLY
01/31/2008 05:38 AM

To Mary E Nilsson/AM/LLY@Lilly
cc Beatrice Grimault/EMA/LLY@Lilly, David G Perahia/EMA/LLY@Lilly
bcc
Subject Re: EU GAD regulatory question

History: This message has been replied to.

Hi Mary,

Looking only at one study is unlikely to produce statistically significant results.
My suggestion is to look at GAD (abrupt vs taper) by dose including anything we have (i.e. for tapering I would include all 4 studies).
I would do the same for MDD (i.e. abrupt vs taper by dose).

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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Answers That Matter.

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Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
30/01/2008 22:11

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc Beatrice Grimault/EMA/LLY@Lilly, David G Perahia/EMA/LLY@Lilly
Subject Re: EU GAD regulatory question

When I was looking at the data, I was focusing on how MDD Taper compared with GAD Taper.
MDD Taper=12.7% v 17.5%
GAD Taper=16.7% v 22.2%

So, I was thinking they were quite similar - GAD a little higher but with both placebo and duloxetine.

The best way to look at GAD Taper versus GAD abrupt is Study HMBR. In the current analyses, GAD abrupt is just from 1 study (HMBR) and GAD Taper is from 4 studies (HMBR being one of them). So, if you use HMBR only, it would be a better comparison. From the HMBR CSR, Table 12.5, the numbers are: Dulox 60 abrupt=31%, Dulox 60 taper=31%, Dulox 120 abrupt=36%, Dulox 120 taper=24%. The statistical tests looked to be insignificant. Numerically, the 120 abrupt versus 120 taper looks different.

HMCB is a MDD study that has both abrupt and taper. It appears that study has an abbreviated report

only, so I'm not finding a table on taper-emergent events. I did find a program but not the output. I'll continue to work on this if necessary. Maybe there's a manuscript on this.

I guess the main question is whether GAD should be tapered differently than MDD. My understanding is that the SPC still says to taper for MDD despite the data.
Anyway, let's discuss this some more.....

By the way - the ouptut below is still in TEST. I will let you know when validation is completed.

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Antonio Stefano Crucitti/EMA/LLY

Antonio Stefano Crucitti/EMA/LLY
01/30/2008 07:23 AM

To David G Perahia/EMA/LLY@Lilly
cc Mary E Nilsson/AM/LLY@Lilly, Beatrice Grimault/EMA/LLY@Lilly
Subject Re: EU GAD regulatory question

Hi David,

Mary provided me with the tables on withdrawal symtpoms in MDD and GAD (abrupt and taper).
My interpretation of these data is that tapering appears much more beneficial in GAD patients than in MDD patients. In fact, in GAD patients treated with placebo, the % of all DEAEs does not change (16.7% tapering disc. vs. 16.2% abrupting disc.) but in duloxetine treated patients the difference is clear (22.2% tapering vs. 33.3% abrupting). Therefore, our position that tapering vs. abrupting is basically the same does not seem applicable in GAD patients.
In MDD patients, abrupting is associated with a higher (twice) frequency of DEAEs in both duloxetine and placebo.

In summary, based on these data I think we should provide a proposal for tapering in GAD patients in the SPC (as requested).

What is your interpretation ?

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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Answers That Matter.

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Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
29/01/2008 15:31

To Antonio Stefano Crucitti/EMA/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Antonio - I believe this is what we want for the new EU GAD question regarding tapering in GAD versus MDD.
I believe we only need the 2 reports addressing tapering and not the 2 reports addressing abrupt discontinuation.
Thoughts?

_____
Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

_____

Wei J Chen/AM/LLY

Wei J Chen /AM/LLY
01/28/2008 04:56 PM

To Mary E Nilsson/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Hi, Mary,

AC Privilege [redacted]

Wei J Chen
433-1469

Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY

01/25/2008 04:38 PM

To Wei J Chen/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

[redacted]
AC Privilege

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Wei J Chen/AM/LLY

Wei J Chen/AM/LLY
01/25/2008 04:18 PM

To Mary E Nilsson/AM/LLY@Lilly
cc
Subject Re: EU GAD regulatory question

Hi, Mary,

[redacted]
AC Privilege

Wei J Chen
433-1469

Mary E Nilsson/AM/LLY

Mary E Nilsson /AM/LLY
01/25/2008 02:06 PM

To Wei J Chen/AM/LLY@Lilly
cc
Subject EU GAD regulatory question

Wei,
Here's the question from the EU:

AC Privilege

[redacted]

Mary E. Nilsson
Senior Research Scientist
Phone: 317-651-8041

Carrie A Krueger/AM/LLY

Carrie A Krueger /AM/LLY
01/07/2008 02:02 PM

To Antonio Stefano Crucitti/EMA/LLY@Lilly, Cynthia Hallberg/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Mary E Nilsson/AM/LLY@Lilly, Melissa Elizabeth Spann/AM/LLY@LILLY, Torkil Fredborg/EMA/LLY@Lilly
cc Diane Mackleston/EMA/LLY@Lilly, James M Russell/AM/LLY@Lilly, Nayan Acharya/AM/LLY@Lilly
Subject GAD Preliminary Response Timeline

Team,
I will be providing project management support for the GAD responses due to EMEA on Feb. 22nd. After discussions with Beatrice, we have created the following timeline for the preliminary and subsequent final responses:

This week - Cynthia to launch shell, begin draft and route to team, analyses work, follow up on action items, Beatrice to talk with Antonio re: safety questions
Monday, Jan. 14th @ 9-10:00 a.m. - next working group meeting
Week of Jan. 14th - proposed analyses to be completed
Jan. 21 - draft preliminary responses complete; consolidated assessment report due to Lilly
Jan. 22-Feb. 8 - review final questions, determine if further analyses needed, formulate final responses
Feb. 11-12 - QC and editorial review, finalize response document
Feb. 13 - sign off/approval
Feb. 14 - to publishing
Feb. 21 - submit to EMEA

Please let me know if you have any questions.

Carrie Krueger
Project Management Associate Consultant, NS Brand Stewardship
317-651-8298 (phone)
317-276-5064 (fax)
kruegercn@lilly.com

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

EXHIBIT 16

David G Perahia /EMA/LLY
07/02/2003 11:36 AM

To Madelaine M Wohlreich/AM/LLY@Lilly
cc John M Plewes/AM/LLY@Lilly, Melissa J Joliat/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nancy Jean Trapp/AM/LLY@Lilly
bcc David G Perahia/EMA/LLY
Subject Re: An obscure question

Cheers, Madelaine - you've hit the nail squarely on the head !

It's not that the discontinuation issue will necessarily be something we can proactively use to sell duloxetine (I believe not, at least from a historical perspective), more that it's something that the media and regulatory authorities might well latch on to unless we are proactive about it. I sense we are being a bit complacent around this, and it could hurt us (e.g. no diffs from parox on abrupt discontinuation in our trials, short t1/2 etc. etc.)

As an opening gambit, I would define proactive as :

(1) Write up our data and get it published as a priority rather than dragging our heels
(2) Consider running a trial which might add to the evidence base on how best to manage stopping the drug, e.g. over how long should drug be tapered ? (open label treatment, then perhaps 3 arms looking at abrupt discontinuation vs. 2 week taper vs. 4 week taper in a double blind fashion, with frequent visits). Good PR due to being open and pushing the science, with an evidence-based recommendation at the end to boot. I'm sure Matt would blanch at this suggestion, but we can't just stick our head into the sand.

Paroxetine is being torn to pieces by the media (and in fact regulators too) over in Europe, and much of the criticism is stemming from the perception that GSK have been, to put it politely, less than transparent about discontinuation with paroxetine and how best to manage it. I would rather we didn't fall into the same trap.

Re : writing resource, I can look into this. I'm certainly willing to offer my services as an author on a manuscript discussing discontinuation with duloxetine, however, and there is the perfect thought leader in the UK (Peter Haddad, who has published pretty widely on the topic in general) to work on it with us.

D.

Madelaine M Wohlreich

Madelaine M Wohlreich
02/07/2003 16:01

To: Michael Detke/AM/LLY@Lilly
cc: David G Perahia/EMA/LLY@Lilly, John M Plewes/AM/LLY@Lilly, Melissa J Joliat/AM/LLY@Lilly, Nancy Jean Trapp/AM/LLY@Lilly
Subject: Re: An obscure question

The feeling here has been that since it will be in our FDA label that tapering is recommended, that there is not a lot more that needs to be done proactively.
When we have said at consulting conferences that discontinuation type side effects could be seen on abrupt taper, clinicians have not appeared to be terribly concerned.

Madelaine
Michael Detke

Michael Detke
07/02/2003 09:47 AM

To: David G Perahia/EMA/LLY@Lilly
cc: Melissa J Joliat/AM/LLY@Lilly, John M Plewes/AM/LLY@Lilly, Nancy Jean Trapp/AM/LLY@Lilly, Madelaine M Wohlreich/AM/LLY@Lilly

Subject: Re: An obscure question

David:

Redacted

Is there any possibility of writing resources in the region/country?

-Mike

Michael J. Detke, M.D., Ph.D.
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285
(317) 277-6420
(317) 276-6026 - fax
mdetke@lilly.com

David G Perahia

David G Perahia
07/02/2003 02:46 AM

To: Michael Detke/AM/LLY@Lilly
cc:
Subject: Re: An obscure question

OK Miguel.

I must confess to being a little unconfortable about the whole discontinuation thing. Maybe it's more of a UK specific issue, but paroxetine is taking a fearsome battering in the media over here at the moment, and a significant part of that is discontinuation-related stuff. It's clear that duloxetine has a significant DESS liability (on abrupt discontinuation, admittedly, but how much taper data do we have yet ?), and the perception will be further reinforced by our short t1/2 which is seen by many as being directly linked (Redacted

Redacted

I've already asked Melissa to look into what publications we have on our "to do" list in this area. If we're not careful, the environment is set for this to blow up in our faces unless we're proactive about it.

Diego.

Michael Detke

Michael Detke
01/07/2003 19:43

To: David G Perahia/EMA/LLY@Lilly
cc:
Subject: Re: An obscure question

David, I think most of the studies checked at one week, and we probably don't have the data broken out in finer temporal intervals than that.

Sorry amigo,

-Miguel

Michael J. Detke, M.D., Ph.D.
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285
(317) 277-6420
(317) 276-6026 - fax
mdetke@lilly.com

David G Perahia

David G Perahia
06/30/2003 11:13 AM

To: Michael Detke/AM/LLY@Lilly
cc:
Subject: An obscure question

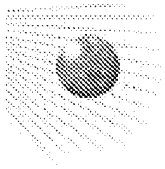
Hi hombre,

Quick question : I was recently asked whether we have any discontinuation data at around 3 days post-discontinuation, this being the time when you might expect maximal symtomatology (approx. 5 half-lives after the final dose). I didn't think we did, but thought I'd check.

Cheers,

David.

EXHIBIT 17



Torkil Fredborg /EMA/LLY
09/23/2008 08:27 AM

To David G Perahia/EMA/LLY@Lilly, Steve Sugino/AM/LLY@Lilly, James Nathaniel Powell/AM/LLY@LILLY, James M Russell/AM/LLY@Lilly, Antonio Stefano Crucitti/EMA/LLY@Lilly
cc David S Thompson/AM/LLY@Lilly, Stephanie de Bono/EMA/LLY@Lilly, Markus R Saba/AM/LLY@Lilly
bcc
Subject URGENT PLEASE READ 20mg SPC proposal from the CHMP

History: This message has been replied to.

Dear all,

The CHMP has considered our response regainding the 20mg application and their request to change the taper language in the SPC.
While we argued not to make any changes, they have proposed the following back to us (new addition underlined):

Discontinuation of treatment
Abrupt discontinuation should be avoided. When stopping treatment with CYMBALTA the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8).If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate. The 30mg and 20 mg duloxetine formulations could be used for this purpose.

While we wanted to avoid the specific mentioning of 20mg in the SPC, I do believe that the proposed wording still offers us flexibility to consider where to market the 20 mg dose (ie. it doesn't imply that that dose must be available in all markets).
I also consider that the addition is very hard to argue since it is accurate and does not actually change the current class labeling.

I would therefore propose that the team accept this addition, with the one caveat that I would propose back to the CHMP to say "20 or 30" instead of "20 and 30".
As previously discussed, we could also suggest a counter proposal, but it is very hard to see what argument we would make.

I will need to get back to the EMEA today, so please respond quickly and I will set us a call later this morning to discuss.

Best regards
Torkil

EXHIBIT 18

Antonio Stefano Crucitti/EMA/LLY@LILLY
02/07/2008 07:24 AM

To Cynthia Hallberg/AM/LLY@Lilly
cc Beatrice Grimault/EMA/LLY@Lilly, CAIRNS@ing.boehringer-ingelheim.com, Carrie A Krueger/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Diane Mackleston/EMA/LLY@Lilly, James M Russell/AM/LLY@Lilly, JENS.CROENLEIN@BC.BOEHRINGER-INGELHEIM.COM, Mary E Nilsson/AM/LLY@Lilly, Melissa Elizabeth Spann/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly
bcc
Subject Re: FYI - EU GAD Q14 has been re-written and a new comparison table added based on new data provided by Mary today

Hi Cynthia,

Q.14: While I agree with the conclusion , I am not convinced that the following sentence is a correct interpretation of the data showed in the table:
"While tapering appears to have decreased the incidence of DEAEs for patients with MDD, the rates of DEAEs observed for patients with GAD were not altered as significantly by tapering."

My interpretation is that tapering has a beneficial effect in both MDD and GAD. We should consider that differently from MDD, the placebo rate for abrupt or taper discontinuation in GAD doesn't change. In duloxetine treated patients there is a decrease from 33% to 22%. The fact that this is mainly driven by 120mg rather than 60mg, also support the beneficial effect of tapering vs abrupting. This would also support the conclusion that we believe the class labeling is approapriate for GAD also.

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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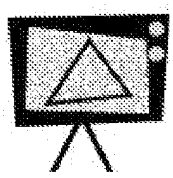
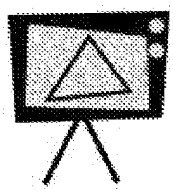
Cynthia Hallberg/AM/LLY



Cynthia Hallberg /AM/LLY
06/02/2008 21:23

To Diane Mackleston/EMA/LLY@Lilly, Beatrice Grimault/EMA/LLY@Lilly, Antonio Stefano Crucitti/EMA/LLY@Lilly, CAIRNS@ing.boehringer-ingelheim.com, David G Perahia/EMA/LLY@Lilly,



JENS.CROENLEIN@BC.BOEHRINGER-INGELHEIM.COM, Mary E Nilsson/AM/LLY@Lilly, Melissa Elizabeth Spann/AM/LLY@LILLY, Carrie A Krueger/AM/LLY@Lilly

cc James M Russell/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly

Subject FYI - EU GAD Q14 has been re-written and a new comparison table added based on new data provided by Mary today

[attachment "Exported Version of 248686-Regulatory Response Second Pub-GAD EU SUBMISSION REG RESPONSE.doc" deleted by Antonio Stefano Crucitti/EMA/LLY]

EXHIBIT 19

Virginia L Wyss/AM/LLY@LILLY
04/10/2006 09:20 PM

To David G Perahia/EMA/LLY@Lilly

cc Beatrice Grimault/EMA/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, Galen Alexander Rudolph/AM/LLY@Lilly, Joachim Wernicke/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Ralf.Rischke@ing.boehringer-ingelheim.com, Richard Bump/AM/LLY@Lilly, S Bret Paulson/AM/LLY@Lilly, Torkil Fredborg/EMA/LLY@Lilly

bcc

Subject Redacted

Redacted

thanks!

Ginny Wyss, CCRA
Associate Consultant, Pharmaceutical Project Management
Du/Flu Product Team
office 317-276-9565
cell 765-346-2158

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David G Perahia/EMA/LLY

David G Perahia /EMA/LLY
04/10/2006 08:49 AM

To Torkil Fredborg/EMA/LLY@Lilly

cc Beatrice Grimault/EMA/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com, Galen Alexander Rudolph/AM/LLY@Lilly, Joachim Wernicke/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Ralf.Rischke@ing.boehringer-ingelheim.com, Richard Bump/AM/LLY@Lilly, S Bret Paulson/AM/LLY@Lilly, Virginia L Wyss/AM/LLY@Lilly

Subject Redacted

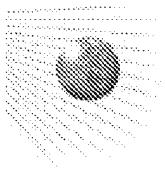
Hi Torkil,

We conducted some additional analyses of our discontinuation data (DEAEs) during the writing of a manuscript on the subject, recently published in the Journal of Affective Disorders. Let me know if you'd like a copy. While the analyses described in the manuscript don't specifically address comparisons between DLX and SSRI comparators, the conclusion is that the "symptom profile is similar to that reported with SSRIs and venlafaxine", i.e. there is little justification for a claim that we differentiate from SSRIs in this regard.

I'm not available tomorrow (en route to Frankfurt), but will be available next Tuesday.

D.

Torkil Fredborg/EMA/LLY



Torkil Fredborg /EMA/LLY
10/04/2006 13:11

To Joachim Wernicke/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Nayan Acharya/EMA/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Virginia L Wyss/AM/LLY@Lilly, BISPHAM@ing.boehringer-ingelheim.com
cc Beatrice Grimault/EMA/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Louise M Spruce/AM/LLY@Lilly, Jose F Gomez/AM/LLY@Lilly, Galen Alexander Rudolph/AM/LLY@Lilly, S Bret Paulson/AM/LLY@Lilly, Ralf.Rischke@ing.boehringer-ingelheim.com
Subject Redacted

All,

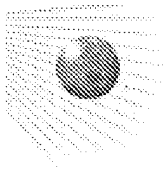
Redacted

In summary, all but one of the issues raised by the Rapporteur concerns actual SPC wording. The exception is a request for "an analysis of the withdrawal symptoms reported on duloxetine discontinuation". This request comes as a reaction to our proposal that the symptoms in the requested class labeling statement have not been reported for duloxetine.

Redacted

Ginny, I would like to discuss the specific request for a withdrawal symptom analysis on the reg response meeting tomorrow, but we might not have time to go through the rest of the list. If not, please would you help set up a meeting later this week or early next (excluding Friday and Monday where the EW office is closed for Easter) to agree on the SPC wording.

Thanks and regards
Torkil
[attachment "SPC - Team comments.doc" deleted by David G Perahia/EMA/LLY] [attachment "duloxetine Rap AR Type II variation (2PSUR) April 2006.doc" deleted by David G Perahia/EMA/LLY]
Torkil Fredborg/EMA/LLY



Torkil Fredborg /EMA/LLY
07/04/2006 18:38

To Virginia L Wyss/AM/LLY, Nayan Acharya/EMA/LLY, Joachim Wernicke/AM/LLY, Michael Detke/AM/LLY, Richard Bump/AM/LLY
cc
Subject Redacted

Dear all,

Redacted

The MAH should provide an analysis of the withdrawal symptoms reported upon duloxetine discontinuation . [the assessor clearly didn't like that we claimed to be different from SSRI's]

Have we got this information ready or is this a new analysis to be prepared?
The reason I need to know is that we need to tell the EMEA if we can respons immediately (within the next couple of week's) or whether we need more time.

Redacted

Best regards - and have a nice weekend!

Torkil

EXHIBIT 20

Antonio Stefano Crucitti/EMA/LLY 08/28/2008 04:16 AM	To	David G Perahia/EMA/LLY@Lilly
	cc	
	bcc	
	Subject	abrupt vs taper discontinuation in duloxetine-treated patients (updated analysis)

History: This message has been replied to.

Hi David,

As pre-annunced last week, please find herewith a table comparing taper vs abrupt discontinuation emergent AEs. The data are from all placebo controlled CTs (datalock is Jan 08- Chronic pain submission).

I identified all DEAEs reported in at least 0.5% of dulox-treated patients (this threshold should appear in either the abrupt or taper dataset). Taper info is black, abrupt info is red highlighted. In addition to the standard statistical values (CMH and Fisher) you will see a D/P rate which stands for dulox/placebo rate (basically it is the % of events with dulox / % of events with placebo. This ratio is supposed to adjust for any placebo effect.

Main results:

1- Of the single events, 28 were found with an incidence of at least 0.5% in either dataset (abrupt or taper).
2- After excluding events not related to duloxetine (see pag 2, i.e. no difference vs. placebo in both subgroups or indication-specific events like depression), 15 DEAEs were identified. Tinnitus (listed in CDS) is on page 2 because it doesn't reach statistical significance in neither abrupt or taper subgroup, though it is very close to significance in the abrupt subgroup.
3- Of the 15 DEAEs, 13 have a Dulox/Placebo rate higher in the abrupt dataset compared with the taper subgroup.
4- When considering all DEAEs, the D/P rate is higher in the taper than in the abrupt subgroup (1.52 vs 1.46); however, when considering the above mentioned 15 drug-related DEAEs pooled, the D/P rate is higher in the abrupt than in the taper subgroup (4.17 vs 3.47).
5- Of the 13 DEAEs with a higher Dulox/Placebo rate in the abrupt subgroup, 5 were statistically more frequent than placebo in the abrupt subgroup but not in the taper subgroup (fatigue, anxiety, irritability, hyperhidrosis, somnolence). There are no events statistically more frequent in the taper but not in the abrupt subgroups.
6- Of note, using a 1% threshold instead of 0.5%, the result doesn't change significantly.
7- I have no data on severity (mild, moderate, severe) but if needed this could also be an interesting analysis to complete the picture.

Take your time to review the data. We can discuss in a couple of weeks in Erl Wood.

Kind regards

Discontinuation Emergent Adverse Events.doc

Antonio CRUCITTI MD
Safety Physician (NS) - Global Patient Safety

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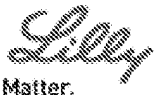

www.lilly.co.uk

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Eli Lilly and Company Limited, a company incorporated in England under company registration number 284 385 and having its registered office at Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL

)iscontinuation Emergent Adverse Events

ll Patients who Entered the Drug-Tapering/Abrupt Phase
lacebo-Controlled Integrated Safety Database

/ent	PLACEBO (N=1641) (N=1166) n(%)	DULOXETINE (N=2141) (N=1582) n(%)	D/P ratio	DULOXETINE VS. PLACEBO p-Value CMH(a)	DULOXETINE VS. PLACEBO p-Value Exact(b)
ATIENTS WITH >=1 DCAE	251(15.3%)	499(23.3%)	1.52	<.001	<.001
ATIENTS WITH >=1 DCAE	259(22.2%)	512(32.4%)	1.46	<.001	<.001
ATIENTS WITH >=1 DCAE (15 events only)	90 (5.5%)	409(19.1%)	3.47	<.001	<.001
ATIENTS WITH >=1 DCAE (15 events only)	87 (7.5%)	495(31.3%)	4.17	<.001	<.001
izziness	11(0.7%)	102(4.8%)	6.85	<.001	<.001
izziness	10(0.9%)	121(7.6%)	8.4	<.001	<.001
eadache	29(1.8%)	58(2.7%)	1.5	.043	.063
eadache	28(2.4%)	78(4.9%)	2.04	<.001	<.001
ausea	12(0.7%)	63(2.9%)	4.14	<.001	<.001
ausea	6(0.5%)	68(4.3%)	8.6	<.001	<.001
iarrhoea	5(0.3%)	33(1.5%)	5	<.001	<.001
iarrhoea	7(0.6%)	29(1.8%)	3	.002	.006
insomnia	4(0.2%)	33(1.5%)	7.5	<.001	<.001
insomnia	12(1.0%)	32(2.0%)	2	.059	.045
atigue	6(0.4%)	16(0.7%)	1.75	.310	.137
atigue	5(0.4%)	16(1.0%)	2.5	.045	.119
nxiety	6(0.4%)	15(0.7%)	1.75	.185	.191
nxiety	6(0.5%)	19(1.2%)	2.4	.039	.069
ertigo	2(0.1%)	16(0.7%)	7	.006	.007
ertigo	0(0.0%)	14(0.9%)	9	<.001	<.001
omiting	3(0.2%)	15(0.7%)	3.5	.031	.029
omiting	4(0.3%)	20(1.3%)	4.3	.009	.012
araesthesia	2(0.1%)	15(0.7%)	7	.010	.012
araesthesia	2(0.2%)	23(1.5%)	7.5	<.001	<.001
critability	4(0.2%)	11(0.5%)	2.5	.187	.296
critability	4(0.3%)	22(1.4%)	4.7	.001	.005
yperhidrosis	4(0.2%)	10(0.5%)	2.5	.138	.295
yperhidrosis	1(0.1%)	17(1.1%)	11	<.001	.001
onormal dreams	0(0.0%)	10(0.5%)	5	.011	.007
onormal dreams	1(0.1%)	13(0.8%)	8	.001	.006
omnolence	2(0.1%)	6(0.3%)	3	.516	.479
omnolence	1(0.1%)	9(0.6%)	6	.027	.051
ightmare	0(0.0%)	6(0.3%)	3	.044	.039
ightmare	0(0.0%)	14(0.9%)	9	<.001	<.001

innitus	3(0.2%)	5(0.2%)	.840	1.00
innitus	8(0.2%)	10(0.6%)	.060	.083
ough	6(0.4%)	10(0.5%)	.647	.802
ough	11(0.3%)	10(0.6%)	.560	.381
epression	0(0.0%)	12(0.6%)	<.001	.002
epression	0(0.0%)	5(0.3%)	.060	.077
yalgia	2(0.1%)	10(0.5%)	.102	.080
yalgia	2(0.2%)	10(0.6%)	.062	.083
nfluenza	8(0.5%)	13(0.6%)	.467	.666
nfluenza	7(0.6%)	9(0.6%)	.958	1.00
ack pain	6(0.4%)	8(0.4%)	.448	1.00
ack pain	12(1.0%)	13(0.8%)	.964	.685
pper respiratory tract infection	12(0.7%)	8(0.4%)	.436	.174
pper respiratory tract infection	6(0.5%)	10(0.6%)	.733	.803
inusitis	11(0.7%)	7(0.3%)	.438	.154
inusitis	6(0.7%)	11(0.7%)	.757	1.00
conchitis	4(0.2%)	6(0.3%)	.864	1.00
conchitis	3(0.3%)	8(0.5%)	.341	.373
nsopharyngitis	11(0.7%)	15(0.7%)	.833	1.00
nsopharyngitis	16(1.4%)	24(1.5%)	.692	.872
naryngolaryngeal pain	3(0.2%)	6(0.3%)	.403	.740
naryngolaryngeal pain	8(0.7%)	9(0.6%)	.836	.807
ry mouth	4(0.2%)	4(0.2%)	.657	.734
ry mouth	4(0.3%)	8(0.5%)	.458	.575
rspepsia	1(0.1%)	7(0.3%)	.115	.149
rspepsia	4(0.3%)	9(0.6%)	.130	.576

EXHIBIT 21

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

JANINE ALI Plaintiff, v. ELI LILLY AND COMPANY, an Indiana corporation, Defendant.	CASE NO.: 1:14-CV-01615

DEFENDANT'S RESPONSES TO PLAINTIFF'S AMENDED FIRST SET OF REQUESTS FOR ADMISSION

Pursuant to Federal Rule of Civil Procedure 36, Defendant Eli Lilly and Company ("Defendant" or "Lilly") hereby submits its responses to Plaintiff's Amended First Set of Requests for Admission, as follows:

GENERAL STATEMENT

The following responses are subject to Lilly's Objections to Plaintiff's Amended First Set of Requests for Admission served on February 23, 2015 pursuant to Federal Rule of Civil Procedure 36 and Local Civil Rule 26 and, for the sake of brevity, not repeated herein. Lilly has not fully completed its investigation of the facts relating to this case, its discovery, or its preparation for trial. Both discovery and independent investigation are ongoing. Therefore, all responses contained herein are based solely upon such information and documents as are both presently available and specifically known to Lilly. Lilly reserves the right to supplement these responses as discovery and this investigation proceed. Lilly's responses are in accordance with

the requirements of the Federal Rules of Civil Procedure, the Local Rules, and any applicable Court Orders.

RESPONSES TO REQUESTS FOR ADMISSION

REQUEST FOR ADMISSION NO. 1:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause adverse symptoms resulting from the discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 1:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta can lead to certain adverse symptoms, as warned in the August 2004 United States Physician Package Insert ("U.S. label") for Cymbalta:

> **WARNINGS**
>
> . . .
>
> If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta (duloxetine hydrochloride), for a description of the risks of discontinuation of Cymbalta).
>
> * * *
>
> **PRECAUTIONS**
>
> . . .
>
> Discontinuation of Treatment with Cymbalta -- Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.
>
> During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus,

and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

* * *

DOSAGE AND ADMINISTRATION

. . .

Discontinuing Cymbalta (duloxetine hydrochloride)

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

This warning has remained largely unchanged since Cymbalta's initial FDA approval for the treatment of Major Depressive Disorder.

REQUEST FOR ADMISSION NO. 2:

Admit that the abrupt discontinuation of a daily dose of 20 mg of CYMBALTA can cause adverse symptoms resulting from the discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 2:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, because Lilly has not comprehensively studied the abrupt discontinuation from the 20 mg/day dose of Cymbalta, and because this low dose is unlikely to present a similar profile than a fully therapeutic dose, denied.

REQUEST FOR ADMISSION NO. 3:

Admit that the abrupt discontinuation of a daily dose of 30 mg of CYMBALTA can cause adverse symptoms resulting from the discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 3:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the abrupt discontinuation of a 30 mg/day dose of Cymbalta may be associated with certain adverse symptoms, which are listed in Cymbalta's U.S. label, but further notes that many such patients do not experience such symptoms upon discontinuation.

REQUEST FOR ADMISSION NO. 4:

Admit that the abrupt discontinuation of a daily dose of 40 mg of CYMBALTA can cause adverse symptoms resulting from the discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 4:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the abrupt discontinuation of a 40 mg/day dose of Cymbalta is associated with certain adverse symptoms, which are listed in Cymbalta's U.S. label, but further notes that many such patients do not experience such symptoms upon discontinuation.

REQUEST FOR ADMISSION NO. 5:

Admit that the abrupt discontinuation of a daily dose of 60 mg of CYMBALTA can cause adverse symptoms resulting from the discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 5:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the abrupt discontinuation of a 60 mg/day dose of Cymbalta is associated with certain adverse symptoms, which are listed in Cymbalta's U.S. label, but further notes that many such patients do not experience such symptoms upon discontinuation.

REQUEST FOR ADMISSION NO. 6:

Admit that CYMBALTA's risk of causing adverse symptoms resulting from discontinuation of CYMBALTA is something a reasonable prescriber would consider important in deciding whether to prescribe the medication.

RESPONSE TO REQUEST FOR ADMISSION NO. 6:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that the risk of the occurrence of adverse symptoms upon discontinuation from an antidepressant like Cymbalta, which is stated in Cymbalta's U.S. label, is one of the many pieces of information that form part of the complex and individualized set of considerations that a medical provider might take into account in deciding whether to prescribe an antidepressant like Cymbalta, although it is likely to not be a major factor given the widespread understanding of this risk across similar medications and the primary goal of the physician to treat the depressive or pain condition affecting the patient at the time of the prescription decision.

REQUEST FOR ADMISSION NO. 7:

Admit that CYMBALTA's risk of causing adverse symptoms resulting from discontinuation of CYMBALTA is something a reasonable person would consider important in deciding whether to purchase and ingest the medication.

RESPONSE TO REQUEST FOR ADMISSION NO. 7:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly cannot reasonably respond to this Request given the inherently unique situation presented for every patient, including the severity of their condition and need for treatment, and the fact that every antidepressant contains similar potential risks arising from the discontinuation of antidepressants like Cymbalta, which is stated in Cymbalta's U.S. label, and it is therefore denied.

REQUEST FOR ADMISSION NO. 8:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause nausea.

RESPONSE TO REQUEST FOR ADMISSION NO. 8:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with nausea, as stated in Cymbalta's U.S. label, although the rate of nausea as observed in the initial short-term clinical trials was low, approximately 5.9 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 9:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause headaches.

RESPONSE TO REQUEST FOR ADMISSION NO. 9:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with headaches, as stated in Cymbalta's U.S. label, although the rate of headaches as observed in the initial short-term clinical trials was low, approximately 5.3 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 10:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause paresthesia.

RESPONSE TO REQUEST FOR ADMISSION NO. 10:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated paresthesia, as stated in Cymbalta's U.S. label, although the rate of paresthesia as observed in the initial short-term clinical trials was low, approximately 2.9 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 11:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause nightmares.

RESPONSE TO REQUEST FOR ADMISSION NO. 11:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with nightmares, as stated in Cymbalta's U.S. label that was in use between 2004 and 2010, although the rate of nightmares as observed in the initial short-term clinical trials was low, approximately 2.0 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 12:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause insomnia.

RESPONSE TO REQUEST FOR ADMISSION NO. 12:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with insomnia, as stated in Cymbalta's U.S. label beginning in 2007, although the rate of insomnia as observed in the initial short-term clinical trials was low, approximately 2.0 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 13:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause anxiety.

RESPONSE TO REQUEST FOR ADMISSION NO. 13:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with anxiety, as stated in Cymbalta's U.S. label, although the rate of anxiety as observed in the initial short-term clinical trials was low, below 2.0 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 14:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause hyperhidrosis.

RESPONSE TO REQUEST FOR ADMISSION NO. 14:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with hyperhidrosis, as stated in Cymbalta's U.S. label, although the rate of hyperhidrosis as observed in the initial short-term clinical trials was low, below 2.0 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 15:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause sensory disturbances.

RESPONSE TO REQUEST FOR ADMISSION NO. 15:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in some patients who are treated with Cymbalta, the gradual or sudden discontinuation of Cymbalta is associated with sensory disturbances, as stated in Cymbalta's U.S. label, although the rate of sensory disturbances as observed in the initial short-term clinical trials was low, below 2.0 percent as reported in the Perahia article.

REQUEST FOR ADMISSION NO. 16:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause suicidal ideation.

RESPONSE TO REQUEST FOR ADMISSION NO. 16:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly responds that it lacks information sufficient to admit this Request, and it is therefore denied. Lilly admits that there had been long-standing concern in the medical community that

antidepressants may have a role in inducing suicidal ideation in certain patients, but a causal relationship has not been established. Studies have not shown an increased risk of suicidal ideation or behaviors in most adult patients treated with Cymbalta compared to those treated with placebo. However, studies show a potential, but not statistically significant, increased risk among young adults (age 18-24). Nevertheless, Cymbalta's U.S. labels warns that "patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases."

REQUEST FOR ADMISSION NO. 17:

Admit that the gradual or sudden discontinuation of CYMBALTA can cause seizures.

RESPONSE TO REQUEST FOR ADMISSION NO. 17:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that there have been postmarketing reports of cases of seizure or seizure-like symptoms after discontinuation of treatment with Cymbalta and other SSRIs or SNRIs, as warned in sections of Cymbalta's U.S. label quoted in Lilly's Response to Request No. 1 and in Section 6.12 (Postmarketing Spontaneous Reports) added to the label in December 2008, but otherwise denied.

REQUEST FOR ADMISSION NO. 18:

Admit that, between 2004 and 2011, LILLY obtained over $17 billion in revenue from the sale of CYMBALTA within the United States.

RESPONSE TO REQUEST FOR ADMISSION NO. 18:

Denied. See https://investor.lilly.com/annuals.cfm for information about annual revenue from the sale of Cymbalta in the United States.

REQUEST FOR ADMISSION NO. 19:

Admit that CYMBALTA has a shorter half-life than Prozac.

RESPONSE TO REQUEST FOR ADMISSION NO. 19:

Admitted.

REQUEST FOR ADMISSION NO. 20:

Admit that CYMBALTA has a shorter half-life than Paxil.

RESPONSE TO REQUEST FOR ADMISSION NO. 20:

Admitted.

REQUEST FOR ADMISSION NO. 21:

Admit that CYMBALTA has a shorter half-life than Zoloft.

RESPONSE TO REQUEST FOR ADMISSION NO. 21:

Admitted.

REQUEST FOR ADMISSION NO. 22:

Admit that CYMBALTA has a shorter half-life than Celexa.

RESPONSE TO REQUEST FOR ADMISSION NO. 22:

Admitted.

REQUEST FOR ADMISSION NO. 23:

Admit that CYMBALTA has a shorter half-life than Lexapro.

RESPONSE TO REQUEST FOR ADMISSION NO. 23:

Admitted.

REQUEST FOR ADMISSION NO. 24:

Admit that Effexor has a shorter half-life than CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 24:

Admitted.

REQUEST FOR ADMISSION NO. 25:

Admit that the shorter the half-life of an SSRI or SNRI, the more frequent the occurrences of WITHDRAWAL.

RESPONSE TO REQUEST FOR ADMISSION NO. 25:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that there is a relationship between the half-life of an SSRI or SNRI and discontinuation symptoms, in which a shorter half-life is one factor in the likelihood of the appearance of discontinuation-emergent adverse events ("DEAEs"), but that half-life does not explain the entire scientific picture.

REQUEST FOR ADMISSION NO. 26:

Admit that Daniel Kajdasz was an employee of LILLY when the PERAHIA ARTICLE was published.

RESPONSE TO REQUEST FOR ADMISSION NO. 26:

Admitted.

REQUEST FOR ADMISSION NO. 27:

Admit that Durisala Desaiah was an employee of LILLY when the PERAHIA ARTICLE was published.

RESPONSE TO REQUEST FOR ADMISSION NO. 27:

Admitted.

REQUEST FOR ADMISSION NO. 28:

Admit that Peter Haddad has received payments from LILLY for attending advisory boards, lecturing, and consultancy work.

RESPONSE TO REQUEST FOR ADMISSION NO. 28:

Admitted.

REQUEST FOR ADMISSION NO. 29:

Admit that YOU never instructed YOUR sales force to distribute the PERAHIA ARTICLE to physicians when it was published in 2005.

RESPONSE TO REQUEST FOR ADMISSION NO. 29:

Lilly is still investigating the nature and extent that the sales force distributed information reflected in the PERAHIA ARTICLE, or the article itself, and thus cannot answer this request at this time.

REQUEST FOR ADMISSION NO. 30:

Admit that, in the six acute treatment placebo controlled trials identified in the PERAHIA ARTICLE, 44.3% of patients receiving CYMBALTA reported at least one discontinuation-emergent adverse event.

RESPONSE TO REQUEST FOR ADMISSION NO. 30:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, 44.3% of patients receiving Cymbalta reported at least one discontinuation-emergent adverse event following abrupt discontinuation and 22.9% of patients receiving placebo reported at least one discontinuation-emergent adverse event.

REQUEST FOR ADMISSION NO. 31:

Admit that, in the six acute treatment placebo controlled trials identified in the PERAHIA ARTICLE, of the 510 discontinuation-emergent adverse events reported, 50.6% were moderate and 9.6% were severe.

RESPONSE TO REQUEST FOR ADMISSION NO. 31:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, of the 510 discontinuation-emergent adverse events reported following abrupt discontinuation from Cymbalta, 39.8% were mild, 50.6% were moderate, and 9.6% were characterized as severe.

REQUEST FOR ADMISSION NO. 32:

Admit that, in the six acute treatment placebo controlled trials identified in the PERAHIA ARTICLE, 3.1% of patients in the CYMBALTA treatment groups withdrew from the studies because of a discontinuation-emergent adverse event.

RESPONSE TO REQUEST FOR ADMISSION NO. 32:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, 3.1% of patients in the Cymbalta treatment groups withdrew from the study due to one or more discontinuation-emergent adverse events following abrupt discontinuation.

REQUEST FOR ADMISSION NO. 33:

Admit that, in the six acute treatment placebo controlled trials identified in the PERAHIA ARTICLE, 62.1% of patients taking 120 mg/day of CYMBALTA experienced at least one discontinuation-emergent adverse event.

RESPONSE TO REQUEST FOR ADMISSION NO. 33:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, 62.1% of patients receiving 120 mg/day of Cymbalta and 22.9% of patients receiving placebo reported at least one discontinuation-emergent adverse event following abrupt discontinuation.

REQUEST FOR ADMISSION NO. 34:

Admit that, in the six acute treatment placebo controlled trials identified in the PERAHIA ARTICLE, of the discontinuation-emergent adverse events reported, 53.7% remained unresolved after two weeks.

RESPONSE TO REQUEST FOR ADMISSION NO. 34:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, 53.7% of discontinuation-emergent adverse events reported by patients receiving Cymbalta were unresolved after two weeks and 52.5% of discontinuation-emergent adverse events reported by patients receiving placebo were unresolved after two weeks when the study concluded, but that the patients continued to remain under the care of their medical providers following the study.

REQUEST FOR ADMISSION NO. 35:

Admit that, in a fifty-two week open-label clinical trial for CYMBALTA identified in the PERAHIA ARTICLE, 50.8% of patients suffered at least one discontinuation-emergent adverse event.

RESPONSE TO REQUEST FOR ADMISSION NO. 35:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the 52-week open-label clinical trial discussed in the PERAHIA ARTICLE, 50.8% of patients receiving Cymbalta reported at least one discontinuation-emergent adverse event following abrupt discontinuation.

REQUEST FOR ADMISSION NO. 36:

Admit that, in a fifty-two week open-label clinical trial for CYMBALTA identified in the PERAHIA ARTICLE, of the discontinuation-emergent adverse events reported, 46.3% were moderate and 17.2% were severe.

RESPONSE TO REQUEST FOR ADMISSION NO. 36:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the 52-week open-label clinical trial discussed in the PERAHIA ARTICLE, of the discontinuation-emergent adverse events reported following abrupt discontinuation, 36.6% were mild, 46.3% were moderate, and 17.2% were characterized as severe.

REQUEST FOR ADMISSION NO. 37:

Admit that, in a fifty-two week open-label clinical trial for CYMBALTA identified in the PERAHIA ARTICLE, of the discontinuation-emergent adverse events reported 55.2% had not resolved after two weeks.

RESPONSE TO REQUEST FOR ADMISSION NO. 37:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the 52-week open-label clinical trial discussed in the PERAHIA ARTICLE, of the discontinuation-emergent adverse events reported, 55.2% had not resolved after two weeks when the study concluded, but that the patients continued to remain under the care of their medical providers following the study.

REQUEST FOR ADMISSION NO. 38:

Admit that LILLY does not know how long it took for the discontinuation-emergent adverse events discussed in the PERAHIA ARTICLE to fully resolve.

RESPONSE TO REQUEST FOR ADMISSION NO. 38:

Denied in part. Lilly admits it knows that of the discontinuation-emergent adverse events reported in the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, 46.3% of those reported by patients receiving Cymbalta and 47.5% of those reported by patients on

placebo resolved within two weeks. Lilly further admits it knows that of the discontinuation-emergent adverse events reported in the two long-term treatment clinical trials discussed in the PERAHIA ARTICLE, 35.3% of those reported by patients receiving Cymbalta resolved within two weeks and 50% of those reported by patients on placebo resolved within one week. Lilly further admits it knows that of the discontinuation-emergent adverse events reported in the 52-week open-label clinical trial discussed in the PERAHIA ARTICLE, 44.8% of those reported resolved within two weeks. Because the trials concluded after the end of two weeks post-discontinuation, the trials did not capture this information from the medical professionals who continued to treat the patients at the conclusion of the trials.

REQUEST FOR ADMISSION NO. 39:

Admit that the work conducted in the PERAHIA ARTICLE was funded by LILLY.

RESPONSE TO REQUEST FOR ADMISSION NO. 39:

Admitted.

REQUEST FOR ADMISSION NO. 40:

Admit that the DEAEs measured in the PERAHIA ARTICLE were assessed by means of spontaneous reports rather than a symptom checklist.

RESPONSE TO REQUEST FOR ADMISSION NO. 40:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that in the trials discussed in the PERAHIA ARTICLE, DEAEs were assessed by means of an open-ended question posed to patients to solicit information about their adverse symptoms and not by means of a symptom checklist in which patients are asked about each specific symptom.

REQUEST FOR ADMISSION NO. 41:

Admit that use of a symptom checklist, instead of spontaneous reports, would be expected to produce higher incidence rates of DEAEs in the PERAHIA ARTICLE.

RESPONSE TO REQUEST FOR ADMISSION NO. 41:

Subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions, Lilly admits that the use of a symptom checklist to measure DEAEs might be expected to produce higher reporting rates of DEAEs for both active treatment and placebo than alternate means of assessment in part due to the suggestive influence of a symptom checklist on patients.

REQUEST FOR ADMISSION NO. 42:

Admit that LILLY sponsored the clinical trial by Jerrold Rosenbaum et al, Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Randomized Clinical Trial, 44 BIOLOGICAL PSYCHIATRY 2, 77-87 (1998).

RESPONSE TO REQUEST FOR ADMISSION NO. 42:

Admitted.

REQUEST FOR ADMISSION NO. 43:

Admit that, in Jerrold Rosenbaum et al, Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Randomized Clinical Trial, 44 BIOLOGICAL PSYCHIATRY 2, 77-87 (1998), the researchers used a symptom checklist to tabulate DEAEs / withdrawal symptoms.

RESPONSE TO REQUEST FOR ADMISSION NO. 43:

Admitted.

REQUEST FOR ADMISSION NO. 44:

Admit that the information contained in the European Medicines Agency Summary of Product Information for CYMBALTA is accurate and true.

RESPONSE TO REQUEST FOR ADMISSION NO. 44:

Admitted subject to Lilly's Objections to Plaintiff's Amended Requests for Admissions.

REQUEST FOR ADMISSION NO. 45:

Admit that, in clinical trials, adverse events seen on abrupt treatment discontinuation of CYMBALTA occurred in approximately 45% of patients treated with CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 45:

Denied in part. Lilly admits that in some clinical trials, specifically the six acute treatment clinical trials discussed in the PERAHIA ARTICLE, discontinuation-emergent adverse events after abrupt discontinuation were reported by 44.3% of patients on active treatment and 22.9% on placebo. In other clinical trials, the incidence of DEAEs was a different rate. For example, in the two long-term treatment clinical trials discussed in the PERAHIA ARTICLE, discontinuation-emergent adverse events after abrupt discontinuation were reported by 9.1% of patients.

REQUEST FOR ADMISSION NO. 46:

Admit that the following statement appears in the European Medicines Agency Summary of Product Information for CYMBALTA: "In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo."

RESPONSE TO REQUEST FOR ADMISSION NO. 46:

Admitted.

REQUEST FOR ADMISSION NO. 47:

Admit that the following statement does not appear on the CYMBALTA LABEL: "In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo."

RESPONSE TO REQUEST FOR ADMISSION NO. 47:

Denied. The above-quoted statement appears in the CYMBALTA LABEL as defined by Plaintiff as "the official prescribing information for the drug, including but not limited to the product insert and medication guides approved by the FDA or other foreign regulatory bodies."

REQUEST FOR ADMISSION NO. 48:

Admit that at no time has LILLY's direct-to-consumer advertising, i.e., television, newspapers, magazines, and/or radio, warned patients that abrupt discontinuation of CYMBALTA occurred in approximately 45% of patients treated with CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 48:

Lilly refers Plaintiff to its objections to this Request.

REQUEST FOR ADMISSION NO. 49:

Admit that the following statement appears in the European Medicines Agency Summary of Product Information for CYMBALTA: "It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2)."

RESPONSE TO REQUEST FOR ADMISSION NO. 49:

Admitted.

REQUEST FOR ADMISSION NO. 50:

Admit that the CYMBALTA LABEL does not state that CYMBALTA should be gradually tapered "over a period of no less than 2 weeks[.]"

RESPONSE TO REQUEST FOR ADMISSION NO. 50:

Denied. The above-quoted statement appears in the CYMBALTA LABEL as defined by Plaintiff as "the official prescribing information for the drug, including but not limited to the product insert and medication guides approved by the FDA or other foreign regulatory bodies."

REQUEST FOR ADMISSION NO. 51:

Admit that the European Medicines Agency Summary of Product Information for CYMBALTA refers to "discontinuation-emergent adverse events" as "withdrawal symptoms."

RESPONSE TO REQUEST FOR ADMISSION NO. 51:

Admitted.

REQUEST FOR ADMISSION NO. 52:

Admit that the following statement appears in the European Medicines Agency Summary of Product Information for CYMBALTA: Withdrawal symptoms "may be prolonged (2-3 months or more)."

RESPONSE TO REQUEST FOR ADMISSION NO. 52:

Lilly admits that Cymbalta's European Medicines Agency Summary of Product Characteristics states, concerning discontinuation-emergent adverse events: "Generally these

symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more)."

REQUEST FOR ADMISSION NO. 53:

Admit that the CYMBALTA LABEL does not estimate how long discontinuation-emergent adverse events will likely take to resolve following abrupt or tapered discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 53:

Denied. An estimate of the duration of discontinuation-emergent adverse events appears in the CYMBALTA LABEL as defined by Plaintiff as "the official prescribing information for the drug, including but not limited to the product insert and medication guides approved by the FDA or other foreign regulatory bodies."

REQUEST FOR ADMISSION NO. 54:

Admit that the CYMBALTA LABEL does not indicate that some individuals may have withdrawal symptoms for 2-3 months or more.

RESPONSE TO REQUEST FOR ADMISSION NO. 54:

Denied. A statement that some individuals may experience prolonged discontinuation-emergent adverse events for 2-3 months or more appears in the CYMBALTA LABEL as defined by Plaintiff as "the official prescribing information for the drug, including but not limited to the product insert and medication guides approved by the FDA or other foreign regulatory bodies."

REQUEST FOR ADMISSION NO. 55:

Admit that the CYMBALTA LABEL does not specify what percentage of patients will likely experience at least one discontinuation-emergent adverse event upon abrupt or tapered discontinuation of CYMBALTA.

RESPONSE TO REQUEST FOR ADMISSION NO. 55:

Denied. A statement of the percentage of patients who reported discontinuation-emergent adverse events in clinical trials appears in the CYMBALTA LABEL as defined by Plaintiff as "the official prescribing information for the drug, including but not limited to the product insert and medication guides approved by the FDA or other foreign regulatory bodies."

REQUEST FOR ADMISSION NO. 56:

Admit that YOU, not the FDA, bear responsibility for the content of the CYMBALTA LABEL at all times.

RESPONSE TO REQUEST FOR ADMISSION NO. 56:

Lilly refers Plaintiff to its objections to this Request.

REQUEST FOR ADMISSION NO. 57:

Admit that the smallest approved dose for CYMBALTA is 20 mg.

RESPONSE TO REQUEST FOR ADMISSION NO. 57:

Admitted.

REQUEST FOR ADMISSION NO. 58:

Admit that CYMBALTA has an elimination half-life of about 12 hours (range 8 to 17 hours).

RESPONSE TO REQUEST FOR ADMISSION NO. 58:

Admitted.

REQUEST FOR ADMISSION NO. 59:

Admit that CYMBALTA should be swallowed whole and should not be chewed or crushed.

RESPONSE TO REQUEST FOR ADMISSION NO. 59:

Admitted.

REQUEST FOR ADMISSION NO. 60:

Admit that the CYMBALTA capsule should not be opened and its contents sprinkled on food or mixed with liquids.

RESPONSE TO REQUEST FOR ADMISSION NO. 60:

Admitted.

REQUEST FOR ADMISSION NO. 61:

Admit that opening a CYMBALTA capsule, or crushing or chewing the CYMBALTA capsule, might affect its enteric coating.

RESPONSE TO REQUEST FOR ADMISSION NO. 61:

Admitted.

Respectfully Submitted,

Dated: March 9, 2015

By: /s/

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Counsel for Eli Lilly and Company

CERTIFICATE OF SERVICE

I, Jeffrey T. Bozman, hereby certify that on the 9th day of March, 2015, I have served Plaintiff's counsel in this action with a copy of Defendant's Responses to Plaintiff's First Set of Requests for Admission by mailing a copy of the same by United States Mail, postage prepaid, and electronic mail to the following address:

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Miller Legal LLC
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Charlottesville, VA 2291
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Dated: March 9, 2015

By: /s/
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